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Original Research Article

Association of SGLT2 inhibitors and urogenital infections in patients attending a tertiary care hospital: a prospective observational study

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ABSTRACT

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are known for efficacy in managing blood sugar levels in type 2 diabetes and also improving cardiovascular and renal outcomes. However, increased risk of urogenital infections (UGIs) remains a significant concern in their safety profile. This study aimed to investigate the association between SGLT2i therapy and UGIs in a real-world clinical set up of a tertiary care centre in India. The key hypothesis was SGLT2i use is associated with incidence of UGIs while the secondary hypothesis included the relationship of the incidence of risk with the dose.
Methods: This was a six-month prospective observational study, that enrolled 309 adults ≥18 years of age, who were newly prescribed SGLT2 inhibitors, particularly Dapagliflozin 5 mg and 10 mg from October 2023. The incidence of UGIs was assessed through patient interviews and medical records during the follow up from 2 weeks of initiation. UGIs were defined as clinical manifestations that resolved on SGLT2i discontinuation or appropriate treatment.
Results: Of 309 initiators, 300 patients were followed up. 9 patients didn't follow up in OPD. From these, 58 (19.3%) patients developed UGIs, comprising of 47 (15.6%) bacterial infections and 11 (3.6%) UGIs of fungal origin. The association was performed on basis of logistic regression analysis which revealed a statistically significant association of UGIs with the prescription of SGLT2i. Higher doses of SGLT2 inhibitors was observed to be associated with significantly increasing the risk of UGIs ($p<0.05$). No significant risk factors such as body mass index (BMI), age, sex, HbA1c or educational status were identified to have significant associations with UGI occurrence.
Conclusions: This study highlights a clinically relevant association between SGLT2i use and urogenital infections.

Keywords: Blood sugar, Dapagliflozin, Diabetes, HbA1c, Mycotic infections, Oral Hypoglycaemics, SGLT2 inhibitors, Urogenital infections, UGI, Bacteriuria, Urethritis

INTRODUCTION

Urogenital infections (UGI)are among the most common complications of Diabetes mellitus (DM).[1] The UGIs are caused commonly by microbial infectants include bacteria such as Escherichia coli, Klebsiella pneumoniae and fungi such as Candida species.[2,3] The prevalence of UGIs among Indian population is reported to be 1.3% for UTI and 5.3% for mycotic infections.[4] Among several therapeutic Oral Hypoglycaemic agents (OHA / OHGA), Sodium-glucose cotransporter 2 (SGLT2) inhibitors (ATC code A10BK) are a relatively recent and novel class particularly used in Type 2 DM. The SGLT2i have demonstrated substantial efficacy in glycaemic control and in improving cardiovascular and renal outcomes in T2DM.[5] However, considering the pharmacological action of SGLT2 inhibitors that promotes elimination of blood sugar to

reduce glycemia, causing glycosuria and thereby increase the risk of urogenital infections(UGI).[6] This association of increased UGI risk is considered to be more prominent with high dose of SGLT2i, probably related to increased glycosuria.[5] Several clinical trials in SGLT2 inhibitors have identified UGIs as one of the most common adverse events.[6] These adverse effects have contributed to drug discontinuation and hospitalization in severe cases. This is particularly relevant as SGLT2 inhibitors exert their therapeutic effects by promoting glycosuria, thereby certainly increasing the risk of genital mycotic infections and urinary tract infections (UTIs).[7]

Previous research has reported an association between SGLT2 inhibitors and UGIs. However, comprehensive studies aiming on these effects in specific populations remain limited.[8] Furthermore, several studies exploring the relationship between SGLT2 inhibitors and urogenital infections, there remains a paucity of comprehensive, region-specific research in this area.[8]

Therefore, the necessity to comprehensively assess the incidence and risk factors associated with urogenital infections in patients receiving SGLT2 inhibitors is significant.[9] This study addresses these gaps by conducting a comprehensive analysis over a six-month period, contributing valuable insights into the epidemiology and clinical implications of urogenital infections associated with SGLT2 inhibitor therapy.[9]

This prospective observational study is designed to provide real-world data on this association, to enhance clinical understanding and patient care. The study aims to specify the region-specific epidemiology of SGLT2 inhibitors associated UGIs and identify and mitigate gaps in the literature particularly for Southern Indian population.[10]

METHODS

This was a prospective observational study. The study was conducted at a tertiary care hospital, Malankara Orthodox Syrian Church Medical College Hospital in Kerala, India.

Inclusion criteria

The study included all patients aged≥18 years who were prescribed SGLT2 inhibitors particularly dapagliflozin for the first time and to be continued as a regular medication. Patients required to provide written informed consent.

Exclusion criteria

The patients with a past history of recurrent urinary tract infections, subjects who were anticipated to have limitations in completing the study or those who refused to sign informed consent or participate were excluded from the study.

All the patients received SGLT2i group medicine, Dapagliflozin (ATC code A10BK01). The study was designed to be an epidemiological observational study, ensuring availability of interfered observations of incidents and progression of UGIs and the real-world data of the risk factors and clinical outcomes.

Sample size determination and data source

The patients attending the OP department receiving SGLT2i for therapy of T2DM, for the first time from October 21, 2023, to January 21, 2024, were enrolled and were followed up them for the next 3 months from initiation. The data included data on exposure (SGLT2 inhibitor use) and outcomes (occurrence of genital mycotic infections and urinary tract infections (UTIs)) in and the study objective was proved using temporal relationships and determine relative risk.

The exposure was defined as time of consumption of SGLT2 inhibitor therapy. The exposure was calculated using difference between date of outcome and date of start of treatment. represented by the variable SGLT2 inhibitor (specifically dapagliflozin) exposure. The outcome was defined as clinical development of urogenital infections or 90 days after the therapy, whichever was earlier.

The epidemiological sample was calculated using Cochran's formula. The research question was–Does SGLT2i therapy for T2DM increase risk of UGIs? Primary hypothesis-the use of SGLT2 inhibitors is associated with increased risk of UGIs

$H_0 = I_E > I_{NE} \pm 4\%$

where IE is incident of UGIs in SGLT2i-exposed population and INE is incident of UGIs of unexposed population. In this 4% is the assumed margin of error.

Null Hypothesis – There is no difference between the risk of UGIs in SGLT2i-exposed population and unexposed population

$H_0\ I_E – (I_{NE} \pm 4\%) = 0$

where IE is incident of UGIs in SGLT2i-exposed population and INE is incident of UGIs of unexposed population. In this 4% is the assumed margin of error. Secondary hypothesis the increased risk, if any is directly influenced by the dosage of the drug

$H_0 IEn > IEn+1$

where IEn is incident of UGIs in lower dose of SGLT2i-exposed population and IEn+1 is incident of UGIs sequentially higher dose of SGLT2i-exposed population. The baseline study data was collected from hospital medical records and laboratory tests. All the eligible patients were contacted and the data was prospectively collected for development of UGIs for three months from

the day of start of SGLT2i therapy. Symptom chart was prepared and used as a checklist.

Exposure and outcome

The exposure variable was the use of SGLT2 inhibitors or dapagliflozin and the outcome variable was urogenital infections. We defined urogenital infections as clinical manifestations and symptoms either described by the patient or diagnosed by the clinician, which show a positive response to anti-fungal or anti-microbial medications. Any symptoms of urogenital infections that developed with SGLT2 inhibitors consumption, followed by their resolution upon discontinuation, were considered as a potential association.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 27. Descriptive statistics including means, frequencies and percentages were used to summarize the data. Inferential statistical tests, such as chi-square tests and logistic regression, were used to analyse the data. The level of significance was set at p value<0.05 and the confidence intervals were set at 95%.

RESULTS

Demographics

The study population exhibited a range of demographic and clinical characteristics. Over half (53%) of the participants were aged 60 years or older, with the next largest age group being those aged 51-60 years (27.3%). Males comprised the majority (64.3%) of the study population. In terms of education level, most participants had completed secondary education (51%), followed by those with an undergraduate degree (25%), primary education (19.3%) and postgraduate education (4.7%). The majority of participants were overweight, with 53.7% having a body mass index (BMI) between 24-30, while 37.7% fell within the normal BMI range of 18-24. Regarding medication dosage, 69.33% of participants were prescribed a 10 mg dose, while 30.66% received a 5 mg dose (Table 1).

Symptomology

Common symptoms in males included abdominal pain (62%, 21/34), burning sensation (44%, 15/34) and painful urination (38%, 13/34), while females experienced itching (58%, 14/24), painful urination (46%, 11/24) and yellowish-white discharge (33%, 8/24). Microbiological analysis identified *Escherichia coli*, *Klebsiella pneumoniae* and Candida species (Figure 1).

Analysis of exposure

Among the 309 SGLT2i initiators, 300 users were followed up. The mean age of the study population was 60.55 years (SD=10.2) and the participants aged 60 years and above were 53%. Males accounted for 64.3% (193/300) of the sample, while females accounted for 35.7% (107/300). Mean BMI was 24.97 (SD=3.5) and mean HbA1c was 8.05% (SD=1.2).

Incidence of urogenital infections

No significant association was found between HbA1c levels and number of infected patients (p<0.05). The incidence of urogenital infections (UGI) was 19.3% (58/300), with a 95% confidence interval (CI) of 14.5-24.1%. Bacterial and fungal infections occurred in 16% (48/300) and 3% (9/300) of the patients, respectively (Table 3 and 4). Males had a slightly lower incidence rate (18%, 35/193) than females 21%, (23/107), although this difference was not statistically significant (p=0.874).

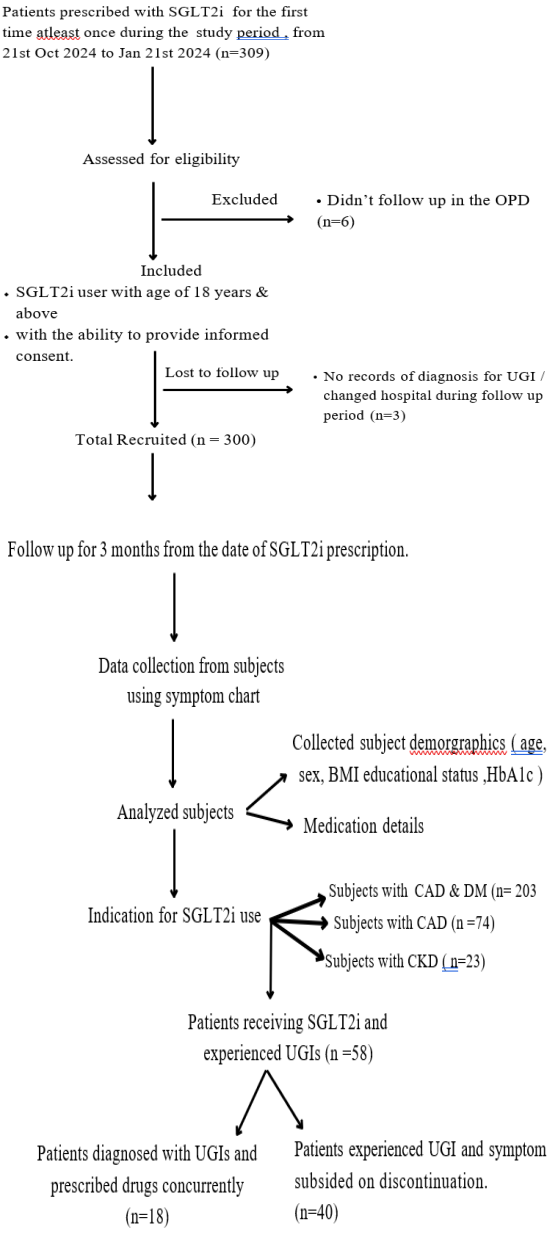

Figure 1: Consort chart.

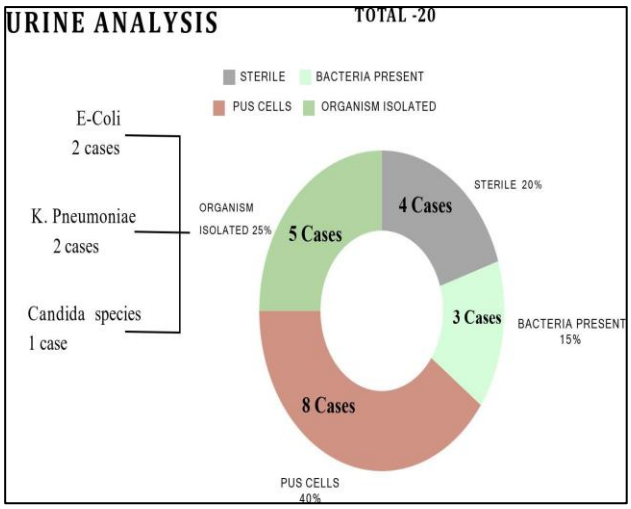

Figure 2: Urine routine and culture tests in urogenital infections.

Primary hypothesis testing

The association between SGLT2 inhibitors and UGIs was tested using logistic regression analysis.

As per the outcomes, the primary hypothesis-the use of SGLT2 inhibitors is associated with an increased risk of urogenital infections (UGIs) in patients attending a tertiary care hospital" was proven with a low type 2 error ($p< 0.05$).

The null Hypothesis (H0) was rejected with a significant confidence interval. The results demonstrated a statistically significant association between SGLT2 inhibitors and UGIs ($p<0.05$).

The incidence of UGIs was 19.3% (58/300), with a narrow 95% confidence interval (CI) of 14.5-24.1%.

Table 1: Baseline characteristics of subjects.

	Category	Total (%)
Age category (years)	21-30	3 (1)
	31-40	18 (6)
	41-50	38 (12.7)
	51-60	82 (27.3)
	60 <	159 (53)
Gender	Male	193 (64.3)
	Female	107 (35.7)
Education	Primary	58 (19.3)
	Secondary	153 (51)
	UG	75 (25)
	PG	14 (4.7)
BMI	<18	7 (2.3)
	18-24	113 (37.7)
	24-30	161 (53.7)
	30 and above	19 (6.3)
Dose	5 mg	92 (30.66)
	10 mg	208 (69.33)
Comorbidities	DM and CAD	203
	CKD	23
	CAD	74

Table 2: Incidence rate of urogenital infections.

Infections	No. of infected	Incidence rate (per 100 Persons)
Urogenital infections	58/300	19.3
Males	35/193	18
Females	23/107	21
Bacterial infection	47/300	15.6
	Males 25/193	12.95
	Female 22/107	20.56
Fungal infection	11/300	3.6
	Males 10/193	0.051
	Females 1/107	0.009

Table 3: Bacterial symptoms in males and females.

Symptoms	Male	Symptoms	Female
Abdominal pain/Pressure or crampingin the lowest abdomen	6	Abdominal pain /Pressure orcramping in the lowest abdomen	6
Back pain or discomfort	3	Back pain or discomfort	5
Burning sensation	9	Burning sensation	2
Cloudy urine / frothyurine	3	Cloudy urine / frothy urine	3
Decreased urine output	2	Decreased urine output	1
Dysuria	6	Dysuria	6
Epididymo-orchitis	1	Fever/ chills	4
Fever/ chills	3	Feeling of incomplete emptyingof the bladder	1
Feeling of incomplete emptying of the bladder	1	Itching	12
Itching	12	Inability to start urine stream	3
Inability to start urinestream	3	Increased frequency of urination	4
Increased frequency ofurination	6	Nausea	1
Redness	5	Redness	2
Swelling	1	Polydypsia	1
Tenderness	2	Polyuria	6
Polydypsia	1	Pyelonephritis	1
Polyuria	1	Painful urination	11
Pyelonephritis	1	Urgency to urinate	4
Prostatic abscess	1	Vomiting	1
Painful urination	9	Urosepsis	1
Pinpoint pain	2		
Urgency to urinate	1		
Vomiting	1		
Urosepsis	1		

Table 4: Symptoms of fungal infections in males.

Symptoms	Males	Females
Itching	12	12
Balanitis/balanoposthitis	10	
Burning sensation	7	
Soreness	8	
Tenderness	6	
Redness	13	
Swelling	9	
Vulvovaginal candidiasis		1
Yellowish-white discharge		7

Table 5: Dose-response relationship.

SGLT2i dose level	Number of infected		Total	Pearson Chi-square	P value
	No	Yes			
5 mg	86 (28.7%)	6 (2%)	92 (30.7%)	13.965	<0.001
10 mg	156 (52%)	52 (17.3%)	208 (69.3%)		
Total	242 (80.7%)	58 (19.3%)	300 (100%)		

Here Pearson Chi-square test is used to test the association between dose level and number of infected patients. The above table shows the frequency distribution of the dose level and number of infected patients. the calculated chi-square value is 13.965 with p value <0.05. So we can conclude that there is a significant association between dose level and number of infected.

Table 6: Wald test for demographic factors associated with urogenital infections.

	B	S.E.	Wald	df	P value	Exp(B)
Constant	-1.597	1.904	0.703	1	0.402	0.202
Age	-0.004	0.014	0.093	1	0.760	0.996
Sex (Male)	-0.232	0.307	0.572	1	0.450	0.793
BMI	-0.021	0.042	0.247	1	0.619	0.979
HbA1C	-0.007	0.083	0.006	1	0.938	0.994
Educational status			1.664	3	0.645	
Educational status (Primary)	1.352	1.142	1.402	1	0.236	3.865
Educational status (Secondary)	1.125	1.100	1.046	1	0.306	3.082
Educational status (UG)	1.268	1.094	1.343	1	0.246	3.553

Table 7: Pearson Correlation for Onset of symptoms in Infected Males and Females.

Onset of symptoms	Total	Males	Females	Chi- square	P value
<30 days	14	8	6		
31-60 days	22	12	10	0.933	0.626
61-90 days	22	15	7		

Secondary and exploratory analysis-dose-response and demographic factors (Table 5)

A significant dose-response relationship was observed with patients receiving 10 mg daily dose having a higher incidence of infections (55.2%, 32/58) than those receiving the 5 mg daily dose (44.8%, 26/58) ($p<0.05$). No significant associations were found between the duration of SGLT2 inhibitor use, age, sex, BMI, educational status and the occurrence of urogenital infections. Logistic regression analysis revealed that only dose was significantly associated with infection risk (OR=1.43, 95% CI=1.03-1.98, $p<0.05$).

DISCUSSION

As prescription of SGLT2 inhibitors is increasingly getting popular for their systemic benefits, recognizing and mitigating their potential adverse effects, including UGIs is a mandate. This observational study identified the risk of urogenital infections in SGLT2i users with an incidence rate of 19.3 % in the population, identifying the risk of both UTI and mycotic infections. The results confirmed that type 2 DM treatment with SGLT2 inhibitors is linked to a higher risk of urogenital infections, with a notable dose-response relationship. Also, there is no signifiable association between demographic factors such as BMI, age and HbA1c with infection risk suggests that the primary determinant of UGI is due to glycosuria rather than patient-specific factors.

While numerous studies have reported similar findings, this study's prospective observational design offers unique insights into the temporal relationship between SGLT2 inhibitor use and the onset of infections. Additionally, the regional specificity of this study provides data that is directly relevant to local clinical practices in India, where factors such as climate, healthcare infrastructure and patient behaviours may influence the incidence of UGIs.[15]

There are contradicting evidences on the association of UTI with prescription SGLT2i for Diabetes. Lega.et.al report increased risk of genital mycotic infections, but demonstrated no an increased risk of UTI.11 Ghosh et.al reported 5 severe UTI and one Acute Kidney Infections. In this study, Ghosh et.al also reported 25.2% incidence of polyuria and 9.4% incidence of genital mycotic infections in 12 months follow up.[12] While both these studies reported that the risk increased was gender-agnostic. However, the mycotic infections appeared to be more common in men, complicating into balanoposthitis and epididymo-orchitis.[11] Mostly, the subclinical period before symptomatic manifestation was up to 30 days of exposure. The added antifungal treatment was required for all the infection, which adds to the medicinal and financial burden to the patients.[12] This study also identified that there was increased burden of Fungal infections in males. However, the study also demonstrated that the risk is present in all genders, not essentially equal, though.

Dave et.al in a 89 cases study of severe UTI, which was corresponding to an incidence rate of 1.86 cases per 1000 person-years of follow up, also demonstrated that there was no increase in risk of UTI events among SGLT2 initiators.[13,14] Though the results are inconsistent to the known risk of UTI our study identified incidence of 15.6% in the 6 months study. However, this study demonstrated higher presence of bacterial UTI symptoms, which included pyelonephritis and urosepsis. Uitrakul et al, in a similar study reported an increased UTI risk focusing on the individual SGLT2I, dapagliflozin, which is also highlighted in other significant studies.10 Other risk

factors such as age, sex, BMI, HbA1c were not observed to be associated with the incidence of UTI.[10] This study also observed no signifiable association of demographic risk factors with UGI. The association of dose with UTI was established by the finding that patients taking 10 mg of dapagliflozin had higher incidence than 5 mg user with a p value of<0.001.

Clinically, the real-world data set of this study is of exceptional relevance to the practice of Diabetes management. This study also highlights the importance of vigilant monitoring and patient education, particularly regarding personal hygiene and symptom recognition.[15]

This study was a short period study, with a single centre set-up, which could establish an understanding of this complex relationship between the SGLT2 inhibitors and UGIs. However, a few outcomes were not statistically significant. Hence, further research in this area is warranted to enhance patient care and outcomes.

CONCLUSION

The Patients treated with SGLT2 inhibitors are at a higher risk of UGIs, especially, the males are more prone to genital mycotic infections. patient hygiene and counselling for preventing urogenital infections (UGI). Patients receiving should be educated about proper genital hygiene practices. In addition, healthcare providers should emphasize the importance of seeking medical attention expediently if symptoms of urogenital infections occur.

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