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The Effect of Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors on Urinary Tract Infections

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Abstract

Objective: Sodium-glucose cotransporter-2 inhibitors are used to treat diabetes by increasing glucose excretion into urine, leading to glycosuria. Although glycosuria increases risk of urinary tract infections, there is a lack of strong evidence showing such an increase with sodium-glucose cotransporter-2 inhibitor use.

Methods: Urine samples from Sodium-glucose cotransporter-2 inhibitor-exposed diabetic patients were inoculated with strains of E. coli (UTI89, LRPF007, and W3110), and bacterial growth was measured using changes in OD600.

Results: Change in OD600 was significantly higher for the nonpathogenic W3110 strain in diabetic patients with history of recurrent urinary tract infections compared to those with no or sporadic history of urinary tract infections. Conclusion: The two uropathogenic strains grew well in urine from all patient groups, possibly due to having defenses against the inhibitory factors in urine that prevent bacterial growth. Sodium-glucose cotransporter-2 inhibitor-exposed patients do not have more Urinary tract infections than the general population because they may have sufficient levels of inhibitory factors to prevent infection.

Keywords: Sodium glucose cotransporter 2; Urinary tract infections; Diabetes; Women's health

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors can be used as a second-line treatment for diabetes by preventing the reabsorption of glucose in the kidney, thereby increasing urinary excretion of glucose [1,2]. However, despite an increased risk of urinary tract infections (UTIs) in patients with glycosuria, our review of trials [3-6] on patients with high glycosuria due to SGLT2 inhibitor use found that there is not a clear consensus on the change of UTI rate in these patients, but generally, findings report low percentages. This surprising observation led us to study bacterial growth in urine from these patients and for a nonpathogenic *E. coli* strain and 2 known uropathogenic *E. coli* (UPEC) strains ex vivo.

Methods

After Institutional Review Board (IRB) approval, type 2 diabetic females aged 18-85 being treated with an SGLT2 inhibitor were recruited from a urology clinic specializing in FPMRS and an endocrinology/metabolism clinic at a tertiary care center and consented. Women were included if they were consistently taking a SGLT2 inhibitor for type 2 diabetes and excluded if they had a urine glucose less than 500 mg/dL on urinalysis or were on antibiotics. A mid-stream urine sample was collected from the patients, analyzed by urinalysis, and frozen at -80°C.

Sample lab analysis: After being thawed, the urines were filtered with a 0.2-micron filter to remove bacterial contaminants. Creatinine level in each urine was measured using a creatinine assay. Single colonies of the uropathogenic *E. coli* (UPEC) strain UTI89 (acute UTI strain), UPEC strain LRPF007 (recurrent UTi strain), and the nonpathogenic laboratory-evolved *E. coli* W3110, were separately grown in 1 mL of Luria-Bertani (LB) broth in a shaking incubator at 4°C for 2 hours. The cells were then collected from the pre-culture, centrifuged, and washed twice with minimal media (specify) to remove nutrients from LB. Each strain was then resuspended to an OD_{600} of 0.02 in phosphate-buffered saline. Two µL of cells were added to 198 µL of the urine and grown in triplicates for 24 hours in a 96-well dish at 37°C with shaking. After the growth period, the lag times, doubling times, colony forming units (CFU) per mL (using OD_{600}), maximum OD_{600}, and change in OD_{600} (max OD_{600} – initial OD_{600}) were measured.

Patient data: Patient data, including demographics, UTI history, and recent antibiotic use, was extracted from EMR (EPIC). Recurrent UTIs (RUTIs) was defined as three symptomatic UTI episodes with culture-proven bacterial strains in the past year or 2 in the past 6 months. [7] Patients were also questioned in office regarding current antibiotic use, antibiotic use in the past 4 weeks, and SGLT2 inhibitor use prior to urine sample collection. The data was analyzed by a third-party researcher uninvolved with patient care. UTI history collected included number of UTIs and documented urine cultures.

Statistics: Values are presented as mean estimates with 95% confidence intervals. Differences between patients with a history of RUTIs compared to patients who have sporadic or never had a UTI were tested using mixed models, with a compound symmetric covariance structure to model repeated measures from the same sample. All tests were completed at the 0.05 significance level without adjustment for multiple comparisons using SAS 9.4 (SAS Institute Inc., Cary NC).

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Results

From 2020 to 2021, 8 women met study criteria. Median age of SGLT2 exposed patients was 63.5 (58.5-65.75), median BMI 31.1 (26.9-35.1), with 6 (75%) not on hormonal supplement, and most were Caucasian (62.5%). Patients were split by UTI history. Three patients had a history of symptomatic RUTIs, while the other 5 had no or sporadic history of UTIs in the past (Table 1) shows a comparison between bacterial growths in these two groups. The 2 UPEC strains, UTI89 and LRPF007, grew to a high density in urine regardless of the patient type. In contrast, W3110 growth (change in OD_{600} and final OD_{600}) was significantly higher in the urine of women with a history of RUTIs (Table 1).

Discussion

A comparison of bacterial growth in urines of SGLT2 patients with and without RUTI history has not been previously reported. All bacterial strains grew faster and to a higher cell density in urine from patients with RUTI history compared to urine from patients with no or only sporadic history of UTIs. The difference reached statistical significance for W3110 growth.

Patients with diabetes face an increased risk of UTIs, with a 1-year incidence of 12.9% in diabetic women. [8] The mechanism behind this risk is not fully understood but is likely a consequence of a combination of diabetic complications, including autonomic dysfunction, and a compromised immune system. [8,9] Glycosuria is another complication of diabetes and occurs due to high concentrations of circulating glucose. SGLT2 proteins contribute to about 90% of filtered glucose reabsorption in the kidney. [1,10] Typically, the glucose reabsorption rate is greater than the influx of filtered glucose such that very little glucose is present in the urine. [11] In diabetics, however, high serum glucose results in a filtered glucose concentration that exceeds the ability for the SGLT2 proteins to reabsorb all of the glucose, leading to glycosuria. [11] SGLT2 inhibitors are a second-line treatment for diabetes. [2] By preventing reabsorption of filtered glucose, less glucose is reintroduced to the body, instead is being excreted in the urine. It would be natural to suspect that diabetic patients on SGLT2 inhibitors would therefore have higher rates of UTIs compared to those not taking this therapy; however, current research indicates mixed results reviews by Donnan et al. [3] and Puckrin et al. [4] both found that despite an increased risk in genital infection, current exposure to a SGLT2 inhibitor did not increase the risk of UTIs aside from with the highest recommended dose of dapagliflozin. A cohort study by Dave et al. [5] found there was also no difference in risk of both severe and non-severe UTIs in patients starting SGLT2 inhibitors compared to those starting DPP-4 inhibitors or GLP-1 agonists, two other diabetes treatments. However, a review by Figueiredo et al. [6] instead found a significant increase in UTI risk when compared to placebo or other oral diabetes medications.

Patients with a history of RUTIs may have a predisposition to having infections compared to those with a sporadic or no history of UTIs perhaps due to a difference in inhibitory factors such as antimicrobial peptides. Bacterial growth is slightly faster in the urines of those with a history of RUTIs as the urinary environment in this population may be more favorable than in urine from patients with no/sporadic history of UTIs. Urine from history of RUTIs patients supported slightly faster growth (although not significantly faster) and more growth (significantly more growth for W3110) than urine from no/sporadic history of UTIs patients. We conclude that the major factor that determines the frequency of UTIs is not nutrient availability but the presence of inhibitory factors, which are diminished in patients with RUTIs. The level of inhibitory factors is likely to be independent of the SGLT2 inhibitors. Therefore, the frequency of UTIs among diabetic patients treated with an SGLT2 inhibitor is likely to be the same as for the general population.

Conclusion

SGLT2 inhibitor use results in glycosuria, which is thought to be

Table 1: Differences between history of RUTI (n = 3) and never/sporadic UTI (n = 5) by strain.

	LRPF007		UTI89		W3110	
	Mean (95% CI)	***P***	**Mean (95% CI)**	***P***	**Mean (95% CI)**	***P***
Growth after 600 mins						
History of RUTI	0.31 (0.19, 0.43)	0.18	0.25 (0.14, 0.37)	0.52	0.20 (0.12, 0.28)	0.076
Never/Sporadic UTI	0.21 (0.12, 0.31)		0.21 (0.12, 0.30)		0.12 (0.05, 0.18)	
Doubling time						
History of RUTI	53.94 (3.63, 104.25)	0.26	56.48 (5.09, 107.86)	0.34	78.86 (-90.34, 248.07)	0.45
Range	33-79.3		41.5-79.3		45.8-124.7	
Never/Sporadic UTI	86.00 (47.02, 124.98)		83.80 (43.99, 123.60)		150.27 (19.21, 281.34)	
Range	37.6-136.6		33.7-138.8		49.4-427.1	
ΔOD_{600}						
History of RUTI	0.29 (0.19, 0.40)	0.14	0.23 (0.13, 0.34)	0.32	0.22 (0.16, 0.28)	0.0074*
Never/Sporadic UTI	0.20 (0.11, 0.28)		0.18 (0.10, 0.26)		0.10 (0.05, 0.14)	
Initial OD_{600}						
History of RUTI	0.02 (-0.04, 0.09)	0.26	0.02 (-0.04, 0.08)	0.23	0.03 (-0.00, 0.06)	0.71
Never/Sporadic UTI	0.06 (0.02, 0.11)		0.07 (0.02, 0.11)		0.04 (0.01, 0.06)	
Final OD_{600}						
History of RUTI	0.32 (0.20, 0.43)	0.38	0.26 (0.15, 0.36)	0.78	0.25 (0.17, 0.32)	0.029*
Never/Sporadic UTI	0.26 (0.17, 0.35)		0.24 (0.16, 0.32)		0.13 (0.07, 0.19)	
Final/Initial OD_{600}						
History of RUTI	19.86 (-2.89, 42.62)	0.66	15.07 (-2.63, 32.77)	0.7	12.56 (3.84, 21.28)	0.14
Never/Sporadic UTI	14.39 (-3.26, 32.04)		11.35 (-2.36, 25.06)		5.00 (-1.76, 11.76)	

associated with higher rates of UTIs due to abundance in nutrients; however, SGLT2 inhibitor use does not confer this increased risk likely due to urinary inhibitory factors against UTIs playing a more substantial role in affecting UTI risk than nutrient availability.

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Conflict of Interest: The authors have no conflicts to disclose.

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