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ORIGINAL ARTICLE

Prevalence of Genitourinary Infections with Sodium Glucose Co-transporter-2 (sglt2) inhibitors in patients with type 2 diabetes

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ABSTRACT

Objectives: The present study was conducted to observe the prevalence of urine and genital infections by the SGLT-2 inhibitors patients with type 2 diabetes

Methods: This multi centre cross sectional study was conducted on type 2 diabetic patients using two different SGLT-2 inhibitors dapagliflozin and empagliflozin either as monotherapy or combination therapy over a period of 03 months from 02-02-2020 to 02-05-2020. The risk of urinary and genital tract infection was assessed on the basis of structured questionnaire performa and medical records.

Results: Out of 615, 296(48%) patients were using dapagliflozin and 319(52%) were using empagliflozin. Male to female ratio in both group were i.e dapagliflozin: 65 %(192) and 35 %(104) empagliflozin 72 %(230) and 28 %(89%) respectively. The risk of urinary infection in dapagliflozin group was 4.3% while it was 6.5% in and empagliflozin. On the other hand the risk of genital tract infection was 3% in dapagliflozin and 4.3% empagliflozin respectively. The prevalence of genital infection was more in female 6(67%) by dapagliflozin and 10(71%) by empagliflozin versus male 3(33%) by dapagliflozin and 4(29%) by empagliflozin respectively. Similarly the prevalence of urinary infection was more in female 8(62%) by dapagliflozin and 14(67%) by empagliflozin versus male 5(38%) by dapagliflozin and 7(33%) by empagliflozin respectively. A significant co relation was found between prevalence of genitourinary infection with female sex and uncontrolled diabetes with p.value 0.001 and 0.003 respectively.

Conclusion: SGLT-2 inhibitors are not associated with increased of risk of genitourinary infection in diabetic patients.

Keywords: SGLT-2 Inhibitors, Dapagliflozin, Empagliflozin, Genitourinary infection

INTRODUCTION

Pakistan stands at 7th position among countries with an increase burden of diabetes according to World health organization (WHO). This burden will expected to reach 11.4 million in 2030 if aggressive steps are not undertaken. The scarce resources in health system may contribute further to increase this burden.[1,2] There are seven groups of antidiabetic drugs discover so far and various drugs are under consideration.[3] Sodium glucose co-transporter-2 (SGLT2) inhibitors are a novel class of oral anti diabetic agents which are used as a monotherapy as well as combination therapy in diabetic patients.[4] The only FDA approved drugs of this group are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.[5] These drugs have excellent safety and tolerability profile with no risk of hypoglycemia.[6] These drugs have promising effects on blood glucose, HbA1C, body weight, lipid profile and blood pressure. In addition these drugs have cardio protective properties by improving endothelial function.[7]

The anti-diabetic effect of Sodium glucose co-transporter-2 (SGLT2) inhibitors is mediated by inhibiting the glucose reabsorption in the proximal convoluted tubule of kidney.[8] The mechanisms of genitourinary infections in diabetic patients may be drug related and non-drug related. Regarding drug related mechanisms, there are about eight groups of antidiabetic drugs to treat patients with T2DM. Out of which SGLT2 inhibitors have major concern about genitourinary infections risk.[9],[10]

People with diabetes have more risk to develop genitourinary infection as compared to non-diabetics.[11] vaginitis is twice more common in diabetic women while balantitis is three times more common in men as compared to non-diabetic.[12] So the present study was conducted to determine the prevalence of genitourinary infections by two SGLT-2 inhibitors (dapagliflozin & empagliflozin) in type 2 diabetic patients

METHODS

This cross sectional study was undertaken at different clinical setting of District Rahim Yar khan. Study approval was got from the Institutional review board (IRB) and written informed consent were taken from all participants before start of the study. Data was calculated from Type 2 diabetic patients taking SGLT-2 inhibitors either as mono therapy or combination therapy over a period of 03 months. Patients without diabetes and gestational diabetes were also excluded from the study.

A structured performa with questionnaire were filled by the medical assistants after taking careful history from the patients and their attendants. Questionnaire was about any signs and symptoms of urine and genital infection during treatment with SGLT-2 inhibitors. Questions were asked about burning pain, urgency, frequency, itching, redness, any discharge, soreness, suprapubic back or abdominal pain, fever with chills, vomiting, dysuria, discomfort at perineal region, costovertebral angle tenderness and sepsis. Patients past history of genitourinary infection before starting SGLT-2 inhibitors was recorded. In addition patient's medical records of routine laboratory tests including blood sugar, HbA1c, lipid

profile, urea, creatinine and urine complete examination were also assessed. Urine culture reports were also assessed in those patients with a history suggestive of genitourinary infections (dysuria, urgency, frequency of urination, suprapubic pain or costovertebral angle tenderness, fever and sepsis). Patients with positive urine culture report without any other possible site infections were categorized in genitourinary infection. Asymptomatic bacteriuria is defended as presence of bacteria in urine without fever. A symptomatic urinary tract infection was defended as presence of bacteria in urine with fever. A patients was labeled significant bacteriuria with presence of $>10^5$ colony-forming units per milliliter of urine.

Statistical package for social sciences (SPSS-18) was used to analyze data. Continuous data were expressed as ± standard deviation. Categorical data were expressed as percentages and frequencies. To see the relationship between two categorical variable Chi- squared test was used. A p-value< 0.05 was considered statistically significant.

RESULTS

A total of 615 patients were enrolled in this observational study. The mean age of the diabetic patient was 38±12 years. About 68% were male and 73% were belonging to urban area. More than 70% patients were from private clinics. The baseline demographic characteristics are shown in table 1.More than half of the patients 319(52%) were on empagliflozin and n=296(48%) were on dapagliflozin. The prevalence of urinary infection in dapagliflozin group was 4.3% while it was 6.5% in empagliflozin group. On the other hand the prevalence of genital tract infection was 3% in dapagliflozin and 4.3% empagliflozin respectively. The prevalence of genital infection was more in female 6(67%) by dapagliflozin and 10(71%) by empagliflozin versus male 3(33%) by dapagliflozin and 4(29%) by empagliflozin respectively. Similarly the prevalence of urinary infection was more in female 8(62%) by dapagliflozin and 14(67%) by empagliflozin versus male 5(38%) by dapagliflozin and 7(33%) by empagliflozin respectively. A significant co relation was found between prevalence of genitourinary infection with female sex and uncontrolled diabetes.

Table 1: Baseline demographic characteristics

Parameters	Total(n=615)
Age(years)	38±12
Sex Male/Female (n-%)	422(68.6%)/193(31.3%)
Urban area	450(73%)
BMI	28.5±5.5
Duration of diabetes (years)	6.4±2.5
HbA1C	7.6±2.2
Patients from Private clinic	455(74%)
Patients from Government Hospital	160(26%)
Duration of treatment with SGLT-2 inhibitors(Months)	4± 1.2
History of previous UTI	33(5.3%)

Table 2: Prevalence of genitourinary infection

Parameters	Group A (Dapagliflozin) n=296(48%)	Group B Empagliflozin n=319(52%)
Genital Infection Male Female	9(3%) 3(33%) 6(67%)	14(4.3%) 4(29%) 10(71%)
Urinary infection Male Female	13(4.3%) 5(38%) 8(62%)	21(6.5%) 7(33%) 14(67%)

Table 3: Co relation of different parameter with genitourinary urinary infections

Parameters	Genitourinary infection(n=57)	p-value
BMI (kg/m2) >30	9(15.7%)	0.23
HbA1c (%) >8.5%	40(70%)	0.003
Duration of Diabetes (years) >5	8(14%)	0.12
Female sex	38(66.6%)	0.001
History of previous UTI	07(12.2%)	0.42

DISCUSSION

Our results showed that dapagliflozin associated prevalence of urinary tract infection were 4.3% and genital infection was 3%. However the risk of genitourinary infections was quite varying in various studies. A study conducted by Bollinder et al. 2012)[13] in type 2 diabetic patients who are having inadequate glycemic control with metformin over a period of 24 weeks. This study reported that risk of urinary and genital tract infection was 6.6% and 3.3% with dapagliflozin as compared to placebo 2.2% and 0% respectively. In another 24 weeks study on type 2 diabetic patients who have inadequate glycemic control with glimepiride. The risk associated with urinary and genital infection was 3.9-6.9% and 3.9-6.9% respectively with dapagliflozin as compared to placebo 6.2% and 0.7% respectively (Strojek et al, 2011).[14]

A 48 week placebo controlled trial revealed the risk of urinary infection was 5.0-8.5% versus placebo 7.9% and genital infection was 8.6-9.2% versus placebo 2.9% at 5mg and 10mg dose of dapagliflozin added on to pioglitazone in type 2 diabetes inadequately controlled on pioglitazone.[15] In another placebo control trial, dapagliflozin associated risk of urinary infection was 6.7% versus 6.3% with placebo and genital infection 9.8% versus 0.4% with over a period of 48 weeks added to sitagliptin with or without metformin.[16] A 102 week trial was conducted on type 2 diabetic patients whose diabetes was inadequately controlled with metformin. This trial showed the risk of urinary tract infection was 8.0% to 13.3% versus placebo 8.0% and genital tract infection 11.7% to 14.6% versus placebo 5.1% at 5 and 10mg of dapagliflozin.[15] In all of the above studies dapagliflozin used as add on therapy in patients with inadequate diabetes control with the first line drugs similar to our study.

In our study the prevalence of genitourinary infections with empagliflozin was (6.5% urinary and 4.3 % genital). A study in type 2 diabetic patients who had inadequate control of diabetes with metformin, the rate of UTI infection was 4.0% with empagliflozin versus 2.8% with placebo and genital tract infection 4.0% with empagliflozin versus 0% with placebo over a period of 12 weeks.[17] A phase 1b placebo controlled trial on 480 type 2 diabetic patients was conducted over of period of 12 week. The urinary tract infection was noted 1.6% by empagliflozin versus 1.2% by placebo and genital tract infections 2% by empagliflozin versus 0% by placebo.[18] Similarly in another placebo controlled trial of 24 week duration at different doses of empagliflozin as add-on to metformin and sulfonylurea in patients with type 2 diabetes., the risk of urinary tract infection were 10.3% (10mg dose), 8.3% (25mg dose)

versus placebo 8% and genital tract infection 2.7% (10mg dose), 2.3%(25mg dose) versus placebo 0.9%. These infection rates were highest in female patients as compared to male.[19]

A long term efficacy and safety profile of empagliflozin, sitagliptin and metformin over a period of 78 week was conducted in type 2 diabetic patients. The risk of urinary tract infections were reported 3.8-12.7 %(empagliflozin), 12.5 %(sitagliptin) and 3.6 %(metformin). Similarly the risk of genital infection was 3.0-5.5 %(empagliflozin), 0 % (sitagliptin) and 1.8 % (metformin) repectively (Schernthaner et al, 2013).

We did not conduct research on canagliflozin as this drug was not available in Pakistan. However study revealed the risk of UTI was 6% with canagliflozin versus 5% with glimepiride over a period of 52 weeks while high rates of genital infection were observed in canagliflozin group 7-8% versus glimepiride 1-2 %(Cefalu et al, 2013) In another comparative study incidence of UTI infection was similar between canagliflozin 4.0% and sitagliptin 5.6% over a period of 52 weeks. However there was high incidence of genital infection 9% in men and 15.3% in women versus sitagliptin 0.5% in men and 4.3% in women. In both studies the risk of genital infection was more in female and at high dose of canagliflozin 300mg.[20]

Data about prevalence of genitourinary infections with SGLT-2 inhibitors are quite varying in various systematic review, meta analysis and clinical studies. Some studies revealed that there is high risk of genitourinary infections with SGLT-2 inhibitors. On the other hand other studies did not find any significant risk compared with control as well as with placebo (Berhan et al. 21and Barker, 2013 ; Zaccardi et al,2016 ; Vasilakou et al,2013 ; Li et al,2017 ; Rudofsky et al,2017; Kawalec et al,2014; Wu et al,2016) . Risk was more common in poorly controlled diabetes; increase BMI, previous history of genitourinary infection and female sex in these studies. However our study found significant correlation with female sex and uncontrolled diabetes.

REFERENCES

1. Zheng Y, Ley SH, Hu FB. Global etiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018; 14(2):88.
2. Hussain A, Ali I. Diabetes mellitus in Pakistan: A major public health concern. Arch Pharm Pract. 2016; 7(1):30-3.
3. Chikara G, Sharma PK, Dwivedi P, Charan J, Ambwani S, Singh S. A narrative review of potential future antidiabetic drugs: should we expect more?. Indian J Clin Biochem. 2018; 33(2):121-31.
4. Dandona, P. and Chaudhuri, A., 2017. Sodium-glucose co-transporter 2 inhibitors for type 2 diabetes mellitus: An overview for the primary care physician. International journal of clinical practice, 71(5), p.e12937.
5. Tat, V. and Forest, C.P., 2018. The role of SGLT2 inhibitors in managing type 2 diabetes. *Journal of the American Academy of PAs*, *31*(6), pp.35-40.
6. Hsia, D.S., Grove, O. and Cefalu, W.T., 2017. An update on SGLT2 inhibitors for the treatment of diabetes mellitus. Current opinion in endocrinology, diabetes, and obesity, 24(1), p.73.
7. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 inhibitors: a review of their antidiabetic and cardio protective effects. Int J Environ Res Public Health. 2019; 16(16):2965.
8. Miller BR, Nguyen H, Hu CJ, Lin C, Nguyen QT. New and emerging drugs and targets for type 2 diabetes: reviewing the evidence. Am Health Drugs Benefits. 2014; 7(8):452.
9. La Vignera, S., Condorelli, R.A., Cannarella, R., Giacone, F., Mongioi', L.M., Cimino, L., Defeudis, G., Mazzilli, R. and Calogero, A.E., 2019. Urogenital infections in patients with diabetes mellitus: Beyond the conventional aspects. International journal of immunopathology and pharmacology, 33, p.2058738419866582.
10. Scheen AJ. SGLT2 inhibitors: benefit/risk balance. Current diabetes reports. 2016;16(10):92.
11. Kumar, R., Kumar, R., Perswani, P., Taimur, M., Shah, A. and Shaukat, F., 2019. Clinical and microbiological profile of urinary tract infections in diabetic versus non-diabetic individuals. Cureus, 11(8).
12. Hirji, I., Andersson, S.W., Guo, Z., Hammar, N. and Gomez-Caminero, A., 2012. Incidence of genital infection among patients with type 2 diabetes in the UK General Practice Research Database. Journal of diabetes and its complications, 26(6), pp.501-505.
13. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. The Journal of Clinical Endocrinology & Metabolism. 2012 ; 97(3):1020-31.
14. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism. 2011;13(10):928-38.
15. Rosenstock J, Vico M, Wei LI, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes care. 2012;35(7):1473-8.
16. Jabbour SA, Hardy E, Sugg J, Parikh S, Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37(3):740-50.
17. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, Woerle HJ. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes, Obesity and Metabolism. 2013;15(12):1154-60.
18. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2013;15(8):721-8.
19. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, Broedl UC, EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care. 2013;36(11):3396-404.
20. Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes care. 2013;36(9):2508-15.
21. Berhan A, Barker A. Sodium glucose co-transport 2 inhibitors in the treatment of type 2 diabetes mellitus: a meta-analysis of randomized double-blind controlled trials. BMC endocrine disorders. 2013 ; 13(1):58.
22. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus:

systematic review and network meta-analysis. Diabetes, Obesity and Metabolism. 2016;18(8):783-94.
23. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR, Tsapas A. Sodium–glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Annals of internal medicine. 2013;159(4):262-74.
24. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism. 2017;19(3):348-55.
25. Rudofsky G, Haenni T, Xu J, Johnsson E. Frequency of Genital Infections According to Body Mass Index in Dapagliflozin-treated Patients with Type 2 Diabetes Mellitus. Experimental and Clinical Endocrinology & Diabetes Reports. 2017;4(01):e1-4.
26. Kawalec P, Mikrut A, Łopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes/metabolism research and reviews. 2014;30(4):269-83.
27. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, Neal B. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. The lancet Diabetes & endocrinology. 2016; 4(5):411-9.