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Original Research Article

To compare the occurrence of urinary tract infection amongst patients of Type 2 DM receiving dapagliflozin monotherapy versus dapagliflozin and sitagliptin combination therapy

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Abstract

Background: Diabetes Mellitus (DM), a chronic metabolic disorder consistently identified by the state of hyperglycaemia. It results due to inability of the body to synthesize insulin, resistance to the action of insulin or both.
Aim: To compare the occurrence of urinary tract infection amongst patients of Type 2 DM receiving Dapagliflozin monotherapy versus Dapagliflozin and Sitagliptin combination therapy.
Objectives: 1) To study the occurrence of urinary tract infection in patients receiving Dapagliflozin monotherapy. 2) To study the occurrence of urinary tract infection in patients receiving Dapagliflozin and Sitagliptin combination therapy 3) To compare the occurrence of urinary tract infection in both groups 4) To study if combination therapy reduces the occurrence of UTI
Materials and Methods: The study was conducted after approval from the Institutional Ethics Committee.
Study design, type, site, duration, number of subjects, and inclusion and exclusion criteria were required and data collected.
Results: This study helped us to study the most commonly reported ADR with the use of newer anti- diabetic drugs.
Conclusion: No significant difference were noted in the incidence of UTI in both groups, showing that combination therapy did not offer any benefit in reducing the risk of UTI.

Keywords: Anti-diabetic drugs, Adverse drug reactions, Urinary Tract Infection

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1. Introduction

Diabetes Mellitus (DM), a chronic metabolic disorder is characterized by persistent hyperglycemia. It results due to inability of the body to synthesize insulin, resistance to the action of insulin or both.

Type 2 Diabetes Mellitus involves 90 – 95% cases of DM.[1] In addition to genetic inheritance, lifestyle factors play a major role in the overall pathogenesis of DM. Smoking, alcohol consumption, physical inactivity and sedentary lifestyle are some of the major modifiable lifestyle factors. Obesity leads to insulin resistance and is the most important risk factor in patients developing type 2 DM.[2] Rightly labelled as a global epidemic, as per statistical analysis by IDF there will be 578 million adults living with Diabetes by 2030. This number is expected to reach or even cross 700 million by the end of 2045.[3] Long standing uncontrolled blood sugar levels are associated with risk of microvascular as well as macrovascular complications. Neuropathy, nephropathy and retinopathy are the major microvascular complications, cerebrovascular and accelerated cardiovascular disease being the major macrovascular complications.[4] Pharmacotherapy aims at lowering blood glucose levels thereby preventing or delaying the occurrence of microvascular and macrovascular complications. Sulfonylureas, Biguanides, Dipeptidyl Peptidase 4 inhibitors (DPP-4is), Thiazolidinedione's (TZDs), Sodium Glucose Co-Transporter2 inhibitors (SGLT-2is), Glucagon Like

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Peptide 1 Receptor Agonists (GLP1RA), Insulins & α-glucosidase inhibitors are the most frequently used classes of drugs in the management of DM.[5] A relatively newer class of glucose lowering drugs, SGLT2is act by reducing reabsorption of glucose from the sodium glucose cotransporter in the proximal convoluted tubule of the kidney. It is generally used in combination with addition of other glucose lowering drugs.[6] Increased concentration of glucose in urine provides a favourable state for bacterial growth and proliferation. Hence, use of SGLT-2is can lead to urinary tract infections (UTIs).[7] Sit gliptin belongs to the class DPP-4is and act by inhibiting the degradation of incretins which are responsible for secretion of insulin and suppression of glucagon. Adverse effects associated with use of Sitagliptin include hedache, rare instances of pancreatitis and allergic reactions. Dapagliflozin and Sitagliptin are available in a fixed dose combination and are known to provide a complementary blood glucose lowering effect with fewer adverse effects.[8-10] Patients taking Dapagliflozin experience urinary tract infection as an adverse effect. The combination of Dapagliflozin and Sitagliptin is also very commonly prescribed when Dapagliflozin alone is unable to control blood glucose levels. Since Dapagliflozin and Sitagliptin act differently, their combination can reduce the amount of glucose excreted in urine when compared to Dapagliflozin alone. Lesser the excretion of glucose in urine, lesser will be the occurrence of urinary tract infection. Our study focused on comparing the occurrence of urinary tract infection in patients receiving either of these two therapies.

2. Review of Literature

In a review article by Konstantinos Papatheodorou et al. “Complications of Diabetes Mellitus” it is mentioned that Diabetes is justly recognized as an emerging global epidemic, representing one of the leading causes of morbidity and mortality worldwide. Hyperglycemia, the common feature of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), can lead to serious complications due to its insidious and chronic nature. In another review article by Andrew B.

Johnson and Roy Taylor titled “Diabetes Mellitus” it has been summarized that in several animal models of autoimmune diabetes, macrophages precede lymphocytes in infiltrating the islets. A review article by Yanling Wu et al. titled “Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention” it has been stated that There are two primary forms of diabetes, insulin-dependent diabetes mellitus (type 1 diabetes mellitus, T1DM) and non-insulin- dependent diabetes mellitus (type 2 diabetes mellitus, T2DM). T2DM is the most common form of DM, which accounts for 90% to 95% of all diabetic patients and is expected to increase to 439 million by 2030. T2DM mostly results from the interaction among genetic, environmental and other risk factors.

Additionally, the progression of T2DM is expedited by the loss of first-phase insulin release, abnormal pulsatility in basal insulin secretion, and heightened glucagon secretion. While T2DM patients typically manage without exogenous insulin, its necessity may arise when blood glucose levels remain poorly regulated despite dietary measures or oral hypoglycemic agents. In addition, people with T2DM are often accompanied by complications, such as cardiovascular diseases, diabetic neuropathy, nephropathy, and retinopathy.[2] Simeon I et al. stated in another review article titled "Pharmacological treatment of hyperglycemia in type 2 diabetes" that Twelve classes of drugs, including biguanides (e.g., metformin), sulfonylureas, thiazolidinediones (TZDs), DPP4is, SGLT2is, GLP1RAs, insulins, α-glucosidase inhibitors, dopaminergic antagonists, bile acid sequestrants, meglitinides, and amylinomimetics, are approved for treating T2D.They also emphasized on the UKPDS study, “The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that enhanced glycemic control is beneficial in T2D. Patients receiving either insulin or sulfonylureas had lower HbA1c levels (7.0% vs. 7.9%) and experienced 12% fewer diabetes-related endpoints, primarily a 25% decrease in microvascular endpoints.[5] A review article by Dhillon et al. titled “Dapagliflozin: In "A Review in Type 2 Diabetes,” findings from various randomized clinical trials were discussed, indicating that numerous randomized, double-blind, multicenter, phase 3 trials have shown the efficacy of dapagliflozin in enhancing glycemic control and decreasing body weight and blood pressure in a diverse range of T2D patients, including those with high baseline HbA1c (≥ 9%) and the elderly (aged ≥ 65 years).Dapagliflozin 10 mg once daily reduces the systolic blood pressure(SBP) and showed improve glycemic control in two phase 3 studies in patients with inadequately controlled T2D and hypertension despite receiving antihypertensive therapy (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy alone or in combination with one other antihypertensive.[6] In a study titled " by Khan et al., “Frequency of Urinary Tract Infections in Type 2 Diabetic Patients Taking Dapagliflozin”, the results of the study stated that “the prevalence of UTIs in diabetic patients receiving either 5 mg or 10 mg of dapagliflozin was 5.3%’’. Women were more affected (76.2%) than men ($p < 0.05$). UTIs were more common among patients over 50 years old (85.7%) than in any other age group. The dose strength of dapagliflozin was not associated with UTIs ($p > 0.05$)”. The possible mechanism is that high glucose levels provide a good environment for bacterial proliferation.[7] A study titled “Efficacy and Safety of Sitagliptin Compared with Dapagliflozin in People ‡ 65 Years Old with Type 2 Diabetes and Mild Renal Insufficiency” by Zhi Jin Xu et al. stated that

Dipeptidyl peptidase 4 (DPP-4) inhibitors are both efficacious and well tolerated throughout the spectrum of renal function, although dose adjustment to regulate drug exposure may be required. In contrast, the sodium-glucose cotransporter 2 (SGLT2) inhibitors have reduced glycemic efficacy in patients with moderate to severe renal insufficiency because of their mechanism of action.

In a retrospective study conducted by Rana Bhattacharjee et al., the study highlighted that "Dapagliflozin and sitagliptin are two anti-diabetic agents that work through different mechanisms to lower blood glucose level. Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduces renal glucose reabsorption, resulting in increased urinary glucose excretion.

Conversely, sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, raises active incretin hormone levels, stimulating insulin secretion while suppressing glucagon secretion. Previous clinical trials have demonstrated that the combination of dapagliflozin and sitagliptin in a fixed-dose formulation offers complementary glucose-lowering effects and maintains a favourable safety profile.The study concluded that the fixed-dose combination (FDC) of dapagliflozin and sit gliptin effectively reduces blood glucose levels and BMI in the Indian population with T2DM while maintaining safety. Clinicians may consider dapagliflozin-sitagliptin FDC as a viable treatment option for T2DM patients.[8]

3. Materials and Methods

The study was conducted after approval from the Institutional Ethics Committee. EC no.- IEC/SSIMS/RP/2023/01

3.1. Study design

It was a prospective, cross-sectional, observational study with duration of 2 months i: e from 17th December 2023 to 17th February 2024. 3.2. Type of study Hospital based study.

3.3. Study site

We conducted the study at one of the Tertiary care Hospital of Central India.

3.4. Study duration

2 months

3.5. No. of subjects/samples that were used

The sample size was 160 patients.

3.6. Inclusion or exclusion criteria

All patients with Type 2 Diabetes Mellitus in the age group of 30 – 70 years who were prescribed Tab. Dapagliflozin 10 mg as add on therapy or combination therapy of Dapagliflozin 10mg + Sitagliptin 100mg with other antidiabetic or Insulin were included in the study.

We excluded catheterized patients, patients who had a history UTI 2 weeks prior to the study and patients with chronic kidney disease (CKD).

3.7. Choice of subjects and control

Patients were divided into 2 groups (Group I and Group 2). Each group consisted of 80 patients.

Group I included patients started on Dapagliflozin monotherapy along with other oral antidiabetic drugs or insulin, whereas Group II included patients started on Dapagliflozin + Sitagliptin combination therapy along with other oral antidiabetic drugs or insulin. Patients reporting symptoms of UTI were advised to give mid-stream urine samples in sterile bottles provided to them. These bottles were then sent for analysis to the microbiology laboratory. We compared the frequency of urinary tract infection in both groups.

3.8. Informed consent procedures

Study participants will be approached in their allotted time period after prior intimation and the researcher will introduce about the ojectives of the research project. After obtaining informed written consent from the study participants they will be approached. An informed consent form was provided to all patients. We designed a questionnaire for the patients through which signs and symptoms of UTI were recorded.

3.9. Sample collection, processing and statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics version 28.0. The data was presented through tables and graphs, further employed frequency, percentage, and descriptive statistics for summarization. To identify associations between nominal/ordinal variables such as the occurrence of UTI, the chi-square test/Fisher exact test was utilized. A significance level of $p < 0.05$ was adopted for statistical significance.v

4. Results

Table 1: Age-wise distribution of study subjects

Age Strata (Years)	Group I	Group II
	Frequencies, n (%)	Frequencies, n (%)
30 - 45	22 (36%)	28 (46%)
45 - 70	38 (63%)	32 (54%)

Table 1: Present the age-wise distribution of study subjects in both groups:

Table 2: Gender wise distribution of study subjects

Gender	Group I	Group II
	Frequencies, n (%)	Frequencies, n (%)
Male	36 (60%)	34 (56%)
Female	24 (40%)	26 (44%)

Table 3: Concomitant Hypertension

	Group I	Group II
Hypertension	Frequencies, n (%)	Frequencies, n (%)
Yes	42 (70%)	44 (73%)
No	18 (30%)	16 (27%)

Table 3 present data on the prevalence of Concomitant hypertension in both groups – Group I and Group II

Table 4: Comparison of UTI Symptoms

UTI symptoms	Group I	Group II	P-Value
	Frequencies, n (%)	Frequencies, n (%)	
Present	09 (15%)	7 (11.6%)	0.788
Absent	51 (85%)	53(88.4%)	

P-Value: (Level of Significance)=(0.728

Table 4 (Figure 4) presents a comparison of urinary tract infection (UTI) symptoms among study subjects who received two different treatments: Dapagliflozin Monotherapy (at a dose of 10mg) and Dapagliflozin combined with Sitagliptin (at doses of Dapagliflozin 10mg and Sitagliptin 100mg).

5. UTI Symptoms Distribution

1. In the Dapagliflozin Monotherapy group, 15% of the subjects have UTI symptoms, while 85% do not.
2. In the Dapagliflozin + Sitagliptin group, 11.6% of the subjects have UTI symptoms, and 88.4% do not.

The p-value associated with the comparison of UTI symptom prevalence between the two treatment groups is 0.788.

This p-value indicates that there is no statistically significant difference in the prevalence of UTI symptoms between the two treatment groups. In other words, the proportions of subjects with and without UTI symptoms are similar across the Dapagliflozin Monotherapy and Dapagliflozin + Sit gliptin groups.

Table 5: Comparison of culture/UTIS

	Group I	Group II	P-Value
Culture/UTIs Positive/Present	Frequencies, n (%)	Frequencies, n (%)	
	05 (8.3%)	4 (6.6%)	0.728
Negative/Absent	55 (91.6%)	56(93.3%)	

Table 5 compares the presence or absence of positive cultures indicating urinary tract infections (UTIs) among study subjects who received two different treatments: Group I (Dapagliflozin Monotherapy (at a dose of 10mg)) and Group II (Dapagliflozin combined with Sitagliptin (at doses of Dapagliflozin 10mg and Sitagliptin 100mg)).

For Dapagliflozin Monotherapy

1. 8.3% of subjects have positive cultures indicating UTIs.

2. 91.6% of subjects have negative cultures indicating no UTIs.

For Dapagliflozin + Sitagliptin

1. 6.6% of subjects have positive cultures indicating UTIs.
2. 93.3% of subjects have negative cultures indicating no UTIs.

The p-value associated with the comparison of positive culture rates between the two treatment groups is 0.728. This suggests no statistically significant difference in the rates of positive cultures indicating UTIs between the two treatment groups.

Our study was conducted on 120 participants, divided into Group I (Dapagliflozin 10mg) + Group II (Dapagliflozin 10mg + Sitagliptin 100mg). 63% of study subjects in Group I and 54% in Group II were in the age group of 45 – 70 years. Out of 60 participants in each group 42 (70%) patients in Group I and 44 (73%) in Group II had concomitant hypertension. Symptoms of urinary tract infection were reported by 09 (15%) patients in Group I and 07 (11.6%) patients in Group II. Urine culture results found out 05 (8.3%) patients in group I and 04 (6.6%) patients in group II to be culture positive.

6. Discussion

Dapagliflozin can be used as monotherapy or as combination therapy along with other antidiabetic drugs in patients with type 2 DM at any stage. Infections in the genitalia are one of the most commonly reported adverse drug reaction associated with use of Dapagliflozin.[13] Sitagliptin on the other hand is a DPP-4 inhibitor, which is widely used in diabetic patients with renal insufficiency.[12]

In our research study we found that 15% patients in Group I reported with signs and symptoms suggestive of UTI whereas 11.6% patients in group II presented with signs and symptoms of UTI.

A research study conducted in the past reported urinary tract infection in 5.7%, 4.3% for Dapagliflozin 5mg and 10mg respectively.[13] In our study a p value of 0.788 concluded that there was no significant difference in the incidence of UTI in Group I and Group II. After results urine culture, we found out that 8.3% of patients in Group I and 6.6% of patients in Group II were found to be culture positive, p value of 0.728 indicating that there was no significant difference incidence of UTI in either of the groups. In a study conducted on the Indian population out of 358 patients receiving combination of Dapagliflozin 10mg + Sitagliptin 100mg, 43 (12.0%) reported urinary tract infection as an adverse event during the 12-week study duration.[8] We also found out that patients. Receiving combination therapy Dapagliflozin 10mg + Sitagliptin 100mg experienced UTI, incidence of which was almost equal to the Dapagliflozin monotherapy group.

7. Conclusion

7.1. Our study ended with the following conclusions

1. Urinary tract infection was the most commonly reported adverse drug reaction in patients receiving Dapagliflozin monotherapy as well as Dapagliflozin + Sitagliptin combination therapy.
2. There was no significant difference in the incidence of UTI in both groups indicating that combination therapy did not offer any benefit in reducing the risk of UTI.
3. None of the patients discontinued drug therapy because of UTI indicating that all cases of UTI were of mild to moderate intensity.

This study helped us to study the most commonly reported adverse drug reactions with the use of newer anti-diabetic drugs. We compared the incidence of UTI after dividing patients into 2 groups and found out that combination therapy did not offer any additional benefit in reducing the risk of UTI.

Ethical No.: IEC/SSIMS /RP/2023/01

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Deshpande AD, Harris-Hayes M, Schoolman M. Epidemiology of Diabetes and Diabetes- Related Complications. *Phys Ther.* 2008;88(11):1254–64.
2. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. *Int J Med Sci.* 2014;11(11):1185–200.
3. Jha RP, Shri N, Patel P, Dhamnetiya D, Bhattacharyya K, Singh M. Trends in the diabetes incidence and mortality in India from 1990 to 2019: a join point and age-period-cohort analysis. *J Diab Metab Disord.* 2021;20(2):1725–40.
4. Forbes JM, Cooper ME. Mechanisms of Diabetic Complications. *Physiol Rev.* 2013;93(1):137–88.
5. Taylor SI, Yazdi ZS, Beitelshees AL. Pharmacological treatment of hyperglycaemia in type 2 diabetes. *J Clin Invest.* 2021;131(2):e142243.
6. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. *Drugs.* 2019;79(10):1135–46.
7. Sarfaraz Khan, Hashmi MS, Rana MA, Zafar GM, Asif S, Farooq MT. Frequency of Urinary Tract Infections in Type 2 Diabetic Patients Taking Dapagliflozin. *Cureus* 2022;14(1):e21720.
8. Bhattacharjee R, Rai M, Joshi P, Prasad A, Birla A. The Real DAPSI: A Real-World Retrospective Study on Assessing the Efficacy and Safety of a Fixed-Dose Combination of Dapagliflozin and Sitagliptin in the Indian Population. *Cureus.* 15(10):e46767.
9. Papatheodorou K, Banach M, Edmonds M, Papanas N, Papazoglou D. Complications of Diabetes. *J Diab Res.* 2015:189525.

10. Johnson AB, Taylor R. Diabetes mellitus. *Postgrad Med J.* 1990;66(782):1010–24.
11. Raji A, Xu ZJ, Lam RLH, O'Neill EA, Kaufman KD, Engel SS. Efficacy and Safety of Sitagliptin Compared with Dapagliflozin in People ≥ 65 Years Old with Type 2 Diabetes and Mild Renal Insufficiency. *Diab Ther.* 2020;11(10):2419–28.
12. Saeed MA, Narendran P. Dapagliflozin for the treatment of type 2 diabetes: a review of the literature. *Drug Des Devel Ther.* 2014;8:2493–505
13. F. Giacco and M. Brownlee, "Oxidative stress and diabetic complications. *Circul Res.* 2010;107;9:1058–70.
14. R. H. Hassan, "Defect of insulin signal in peripheral tissues: important role of ceramide. *World J Diab.* 2014;5(3):244–57

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