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# The Effects of Dapagliflozin Therapy on Serum Uric Acid Levels in Patients of Type 2 Diabetes Mellitus with Hyperuricemia

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## ABSTRACT

***Objective:*** To assess the impact of Dapagliflozin on Serum Uric Acid levels in patients of Type-2 Diabetes Mellitus having hyperuricemia.

***Study Design:*** Quasi-Experimental Study.

***Place and Duration of Study:*** Medicine Department of Tertiary Care Hospital Rawalpindi, Pakistan, from Sep 2023 to Sep 2024.

***Methodology:*** In this study, participants were categorized into two different groups. Individuals in Group-A received Dapagliflozin 10 mg/d in conjunction with their standard glucose-lowering medications, while those in Group-B proceeded with regular glucose-lowering medications. Baseline physical examinations, as well as blood samples, were collected from all the subjects of both groups, and then these were performed again after the 12, 24, as well as 48 weeks of treatment.

***Results:*** A total of 250 participants were enrolled in this study. Our study results indicate that after 48 weeks, the mean serum Uric Acid level decreased significantly by 28.0µmol/L in Group-A, while there was no change in Group-B (0.0 µmol/L), which was statistically significant ($p$<0.001). For HbA1c levels, the Group-A had a mean reduction of 1.40%, compared to a 1.46% reduction in the glucose-lowering medications group, which was not significant ($p$=0.47).

***Conclusion:*** Dapagliflozin reduced serum Uric Acid levels in Type 2 Diabetes Mellitus patients with hyperuricemia as opposed to glucose-lowering medication alone.

**Keywords:** Dapagliflozin, Glucose-Lowering Drugs (GLDs), Hyperuricemia, Type 2 Diabetes Mellitus.

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## INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic condition marked by insulin resistance in key insulin-responsive tissues such as the fat tissue, liver, and skeletal muscles, along with insufficient insulin production from the pancreatic β-cells.[1] In 2021, the worldwide prevalence of diabetes mellitus was estimated to be 10.5%. Researches indicate that by 2045, this number may increase to 12.2%, potentially impacting around 783.2 million people.[2] Additionally, diabetes contributed to 9.9% of deaths from all causes for individuals aged 20 to 99 globally, placing a considerable burden on healthcare systems around the world.[3,4]

Serum Uric Acid levels are generally higher in individuals with diabetes when compared to those who are healthy.[5-7] A prior study involving 17,044 individuals in China indicated that the elevated Uric Acid levels were connected to T2DM after accounting for possible confounding factors.[8] Another follow-up study conducted over 15 years found that, compared to normal SUA levels, hyperuricemia was independently linked to a 1.25-fold increase in pre-diabetes, a 1.36-fold increase in insulin resistance, and a 1.87-fold increase in T2DM.[9] Moreover, hyperuricemia was identified as a causative agent of worsening diabetic peripheral neuropathy, elevating the risk of cancer, higher mortality rates, metabolic syndrome, and atrial fibrillation in individuals diagnosed with T2DM.

Considering the negative impacts of hyperuricemia, it has been suggested that decreasing serum Uric Acid (SUA) levels could be advantageous for individuals with type 2 diabetes mellitus (T2DM). Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2). It was the first SGLT2 inhibitor to receive approval for the treatment of T2DM.[10] Notably, several studies have reported that Dapagliflozin can effectively reduce SUA levels. This study aimed to assess the impact of the Dapagliflozin on Serum Uric Acid levels among patients of T2DM along with hyperuricemia at our setup.

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## METHODOLOGY

This Quasi-experimental study was performed at the Medicine Department of Tertiary Care Hospital, Rawalpindi, from September 2023 to September 2024. After getting approval from the Institutional Review Board (Reference Number 704).

**Inclusion Criteria:** Adult patients of either gender diagnosed with T2DM for over 18 years ago, had no contraindications to sodium-glucose cotransporter 2 (SGLT2) inhibitor, and had a serum Uric Acid level higher than 357µmol/L were included.

**Exclusion Criteria:** Patients with other forms of diabetes mellitus, those experiencing acute complications of Type 2 Diabetes Mellitus (T2DM), those currently being treated with the SGLT2 inhibitors as well as medications that lower Uric Acid levels such as febuxostat, or allopurinol had significant liver or kidney issues, diagnosed with cancer or other serious health conditions, and those who pregnant or breastfeeding were excluded.

We calculated a sample size of 171 using the WHO calculator, keeping the prevalence of Type 2 Diabetes Mellitus with hyperuricemia at 12.7%.[11] But we ultimately included 250 patients using random sampling.

Informed written consent was secured prior to the enrollment of all participants, and their privacy was maintained throughout the process. The participants were categorized into two different groups. Those in the treatment group (Group-A) received Dapagliflozin 10 mg per day in conjunction with their standard glucose-lowering medications (GLDs). In contrast, participants in the control group (Group-B) proceeded with their regular glucose-lowering medications only. Patient flow can be seen in Figure-1. These glucose-lowering medications included α-glucosidase inhibitors, metformin, glinides, glucagon-like peptide-1 receptor agonists (GLP-1RA), sulfonylureas, glitazones, dipeptidyl peptidase 4 inhibitors (DPP-4i), and insulin. The dosages of these medications were modified based on blood glucose levels at fasting condition as well as the random blood glucose levels, monitored through self-testing.

Baseline physical examination as well as blood samples were collected from both groups for the relevant tests. Then these were performed repeatedly after 12, 24, as well as 48 weeks of the treatment. Medical history was reviewed for baseline data as well as for each clinic visit, documenting information such as height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Measurements including HbA1c, fasting blood glucose (FBG), as well as serum Uric Acid (SUA) levels were also noted. Micro-vascular and macro-vascular complications due to the medication were also assessed in both the groups. The BMI value (Body mass index) was determined using weight in kilograms divided by height in meters square ($m^2$).

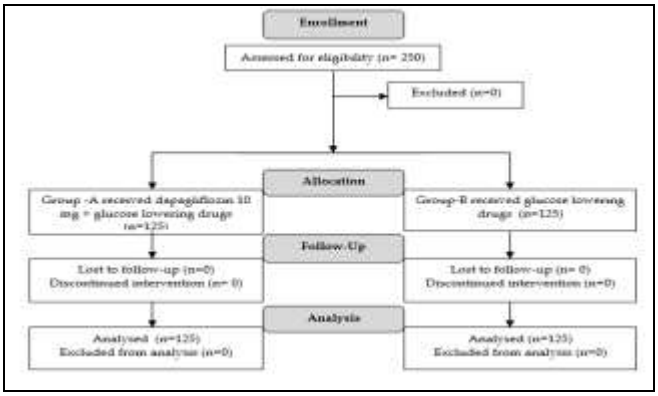


**Figure-1: Patient Flow Diagram (n=250)**

Statistics Package for Social Sciences (SPSS) version 24 was utilized for data analyses. Continuous variables were initially analyzed for normality with the help of the Shapiro-Wilk Test. For normally distributed data, values were presented as Mean±SD, and as median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. For comparison of characteristics across groups, the Mann-Whitney U-test was employed for non-parametric variables and independent t-test for parametric variables. Chi-square test was used for categorical variables. A *p*-value of less than 0.05 was considered statistically significant.

## RESULTS

Of the 250 individuals who were included in this study, 125 received daily Dapagliflozin 10 mg therapy in combination with routine glucose-lowering medications (Group-A), while the other 125 received glucose lowering drugs (GLDs) only (Group-B). The baseline, as well as the demographic features that include the age, DBP, BMI, SBP, diabetes duration, serum creatinine as well as HbA1c, were similar across groups ($p>0.05$). The incidence of hypertension ($p=0.034$), microvascular complications ($p<0.001$) and macro-vascular complications ($p<0.001$) was significantly higher in Group-A. Total cholesterol

levels were significantly higher in Group-B compared to Group-A (p=0.033). Baseline Serum Uric Acid levels appeared to be similar between the two groups ($p$= 0.364).

**Table-I: Baseline and Demographic features across Groups (n=250)**

| Variables | Group-A n=125 n (%) | Group-B n=125 n (%) | *p*-value |
|---|---|---|---|
| Gender (males) | 66 (55.9%) | 52(44.1%) | 0.050 |
| Hypertension | 85 (54.8%) | 70(45.2%) | 0.034 |
| Macro-vascular complications | 79 (72.5%) | 30(27.5%) | <0.001 |
| Microvascular Complications | 19 (90.5%) | 2 (9.5%) | <0.001 |
| Age (years) | 56.98±12.42 | 57.03±12.13 | 0.975 |
| BMI (kg/m2) | 26.34±4.67 | 26.45±4.66 | 0.854 |
| Height (cm) | 163.0 (153.5-177.0) | 165.0 (156.0-176.5) | 0.323 |
| Weight (kg) | 71.80 (66.55-78.70) | 73.30 (67.60-79.15) | 0.532 |
| Total Cholesterol (mmol/L) | 4.20 (3.00-5.45) | 4.30 (3.75-5.95) | 0.033 |
| Triglycerides (mmol/L) | 1.50 (1.15-1.90) | 1.70 (1.20-2.20) | 0.079 |
| Serum creatinine (µmol/L) | 63.10 (52.30-69.20) | 60.20 (47.10-69.60) | 0.966 |
| Serum Uric Acid (µmol/L) | 408.0 (378.0-439.0) | 413.00 (383.0-443.0) | 0.364 |
| Systolic Blood Pressure (mmHg) | 135.0 (115.0-162.5) | 137.00 (125.0-152.5) | 0.764 |
| Diastolic Blood Pressure (mmHg) | 85.00 (78.0-95.0) | 85.00 (79.0-95.0) | 0.889 |
| HBA1c (%) | 8.00 (6.3-9.4) | 7.80 (6.5-8.9) | 0.208 |

Table-II presents data comparing serum Uric Acid (SUA) levels and HbA1c values between the two groups over time. At baseline, Serum Uric Acid levels appeared to be similar between the two groups, with median values of 408.0 µmol/L in Group-A and 413.0 µmol/L in Group-B ($p$=0.364). However, at 12 weeks, 24 weeks, and 48 weeks, SUA levels were significantly lower in the Dapagliflozin group compared to the control group ($p$<0.001 for all time points). By 48 weeks, the median SUA decreased to 380.0µmol/L in the Dapagliflozin group, while it remained higher at 410.0µmol/L in the GLDs only group.

For HbA1c, no significant differences were observed between the two groups at baseline ($p$=0.208) or at any of the subsequent time points (12 weeks, 24 weeks, and 48 weeks). Both groups demonstrated reductions in HbA1c over time, but the changes were not statistically different.

Table-III compares the effects of Dapagliflozin combined with GLDs (Glucose-Lowering Drugs) versus GLDs alone on serum Uric Acid levels and HBA1c over 48 weeks. In Group-A, the mean serum Uric Acid level decreased significantly by 28.0µmol/L. In comparison, Group-B showed no change (0.0 µmol/L), having a $p$-value of <0.001, indicating a statistically significant difference. For HbA1c levels, Group-A had a mean reduction of 1.40%, compared to a 1.46% reduction in Group-B ($p$=0.471). This suggests that while Dapagliflozin significantly reduces serum Uric Acid levels, it does not significantly impact HbA1c levels compared to GLDs alone.

**Table-II: Comparison of Serum Uric Acid and HbA1c levels Between Groups over Time (n=250)**

| Serum Uric Acid | Group-A n=125 (Median, IQR) | Group-B n=125 (Median, IQR) | *p*-value |
|---|---|---|---|
| Baseline | 408.0 (378.0-439.0) | 413.0 (383.0-443.0) | 0.364 |
| 12 weeks | 391.0 (350.0-415.0) | 415.0 (390.0-444.0) | <0.001 |
| 24 weeks | 395.0 (350.0-419.5) | 418.0 (390.0-445.0) | <0.001 |
| 48 weeks | 380.0 (334.5-405.0) | 410.0 (383.0-440.0) | <0.001 |
| **HBA1c** | | | |
| Baseline | 8.00 (6.30-9.40) | 7.80 (6.50-8.90) | 0.208 |
| 12 weeks | 7.00 (5.45-8.00) | 6.60 (5.50-7.70) | 0.401 |
| 24 weeks | 6.60 (5.25-7.60) | 6.30 (5.30-7.40) | 0.587 |
| 48 weeks | 6.5 (5.15-7.50) | 6.2 (5.20-7.30) | 0.598 |

**IQR: Inter-Quartile Range*

**Table-III: Differences in Serum Uric Acid and HbA1c levels at 48 weeks Compared to Baseline Across Groups (n=250)**

| | Group-A n=125 | Group-B n=125 | *p*-value |
|---|---|---|---|
| Difference in Serum Uric Acid Level at 48 weeks with respect to baseline | 28.0 (13.00-57.50) | 0.0 | <0.001 |
| The difference in HbA1c at 48 weeks with respect to baseline | 1.40 (1.80-1.10) | 1.46 (-0.80-3.00) | 0.471 |

## DISCUSSION

Dapagliflozin is an SGLT2 inhibitor known to enhance glycemic control effectively, either by itself or in combination with other antihyperglycemic medications such as metformin, insulin, or sitagliptin, while maintaining an acceptable level of safety and tolerability through an insulin-independent approach in various randomized controlled trials.[12,13] The proposed mechanisms of action may involve a

reduction in glucose reabsorption within the proximal tubule, leading to increased glucose elimination in the urine. Alongside its blood sugar-lowering effects, Dapagliflozin has also demonstrated additional advantages, such as potential improvements in cardiovascular health, overall weight loss, decreased blood pressure, and lower serum Uric Acid levels.[14]

Various clinical studies concluded that Dapagliflozin combined with GLDs has a strong potential to reduce the serum Uric Acid level as compared to the alone GLDs medications. Our study results found that the serum Uric Acid level decreased by 17µmol/L after 12 weeks, 13µmol/L after 24 weeks and 28µmol/L after 48 weeks from the baseline value in the Group-A (Dapagliflozin plus glucose lowering drugs) as compared to alone Group-B (glucose lowering drugs alone) in which serum Uric Acid level remained the same. Similar to our study, Jabbour *et al*.,[15] also performed a study to find the effect of Dapagliflozin on the serum Uric Acid level and found that 10mg dose of Dapagliflozin daily can reduce 44.63µmol/L of SUA after 24 weeks and 45.22µmol/L of SUA after 48 weeks which showed that Dapagliflozin has significant effect on lowering the SUA level. Another study by K. Strojek *et al*.[16] also concluded the reduction level of SUA of 26.18µmol/L after 24 weeks by using a 10mg dose of Dapagliflozin. Bailey *et al*.[17] also studied the Dapagliflozin effect and found 52.9µmol/L decreases in SUA level after 102 weeks of treatment with a 10 mg dose.

Several meta-analyses reinforce the capacity of Dapagliflozin to lower Uric Acid levels. One meta-analysis encompassing 55 studies reported a weighted mean difference (WMD) of 35.17µmol/L (95% CI 30.66–39.68) for Dapagliflozin's effect on decreasing SUA levels.[18] Additionally, a review of 62 studies indicated a WMD of 36.99µmol/L (95% CI 32.25–41.73).[19] Xin *et al*.[20] analyzed 31 studies, revealing a WMD of 38.05µmol/L (95% CI 31.62–44.47).

Another finding of our study included the effect of Dapagliflozin and GLDs on HbA1c levels. The baseline value of HbA1c in Group-A was 8%, and in Group-B was 7.80%. In Group-A this value reduced to 7% after 12 weeks, 6.60% after 24 weeks, and 6.5% after 48 weeks, while in Group-B, it reduced to 6.60% after 12 weeks, 6.30% after 24 weeks, and 6.2% after 48 weeks. There was no statistically significant difference across groups. In one similar study, the baseline value of HbA1c was 8.0% in the Dapagliflozin group and 7.7% in the control group. This value was reduced to 6.9% after 12 weeks, 6.7% after 24 weeks, and 6.6% after 48 weeks in the Dapagliflozin group, while in the control group, the value from the baseline decreased to 6.6% after 12 weeks, 6.4% after 24 weeks, and 6.3% after 48 weeks. This suggested that Dapagliflozin did not have any additional HbA1c lowering properties.[20]

## LIMITATIONS OF THE STUDY

Our study had certain limitations. Firstly, apart from Dapagliflozin, the potential impact of other co-administered hypoglycemic agents on serum Uric Acid levels might have influenced the findings. Secondly, the relatively small sample size restricts generalizability of results. Lastly, the study featured a brief follow-up period, due to which certain indicators could not be studied.

## CONCLUSION

Dapagliflozin reduced serum Uric Acid levels in Type 2 Diabetes Mellitus patients with hyperuricemia as opposed to glucose-lowering medication alone.

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**Authors Contribution**

Following authors have made substantial contributions to the manuscript as under:

EM & MNQ: Conception, study design, drafting the manuscript, approval of the final version to be published.

FAS & FH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

KAS & LY: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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