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Efficacy and Safety of Dapagliflozin in Type 2 Diabetics with Stage 3A Chronic Kidney Disease

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Author`s Contribution

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ABSTRACT

Objective: To evaluate the efficacy and safety of Dapagliflozin that is a sodium-glucose co-transporter 2 (SGLT2) inhibitor in patients with chronic kidney disease stage 3A (CKD 3A) and inadequately managed Type 2 Diabetes Mellitus (T2DM).

Methodology: The randomized controlled trial study was conducted at PIMS Islamabad from January 2022 to December 2022, included 196 patients with T2DM and CKD 3A (eGFR 45-60 ml/min/m²) with inadequate glycemic control (HbA1c 7.0%-11.0%). Patients were assigned to Dapagliflozin 10 mg/day (Group A) and placebo plus standard care (Group B), randomly. After 24 weeks of treatment the HbA1c, eGFR and hypoglycemic events were measured at baseline. Change in HbA1c was used to measure efficacy and safety was evaluated by eGFR changes and hypoglycemic episodes.

Results: Group A showed a reduction in HbA1c levels after 24 weeks with a mean decrease from 8.2% (± 0.71) to 7.7% (± 0.68) ($p = 0.002$). Group B showed no significant change with a mean HbA1c decreasing from 7.58% (± 0.72) to 7.52% (± 0.38). The eGFR in Group A decreased from 52.14 ml/min/m² (± 4.8) to 51.27 ml/min/m² (± 5.8) and in Group B a decline from 50.8 ml/min/m² (± 6.7) to 47.6 ml/min/m² (± 6.0) ($p < 0.000$) was observed. In 5% of patients in Group A and 6% in Group B hypoglycemic episodes occurred and there was no significant difference found between the groups in terms of hypoglycemic episodes.

Conclusion: Dapagliflozin effectively reduced HbA1c with no significant impact on eGFR or hypoglycemic events. It can be considered a safe and efficacious treatment option for T2DM patients with CKD 3A.

Keywords: Diabetes Mellitus Type 2, SGLT2 inhibitor, Dapagliflozin, CKD 3A, HbA1c, eGFR, hypoglycemia.

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Introduction

Diabetes mellitus is a prevalent global health issue which affects approximately 9.3% of the world's population.[1] Diabetes has a significant impact on kidneys with 40-45% of diabetic patients developing varying stages of renal dysfunction.[2] Diabetes is responsible for 20-30% of end-stage renal disease (ESRD) cases.[3]

In patients with chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of 15-60 mL/min/m² (stages III-IV KDIGO) it is recommended to maintain an HbA1c level between 6.5-8% to improve renal function. Metformin is the primary treatment for type 2 diabetes mellitus (T2DM) but it is contraindicated in patients with eGFR below 30 mL/min/m² due to the risk of lactic acidosis.[4] Insulin secretagogues such as dipeptidyl peptidase-4 inhibitors require dose adjustments due to renal excretion other than linagliptin.[5] These agents are associated with an increased risk of hypoglycemic episodes in patients with CKD.[6]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors offer a mechanism by reducing serum glucose levels through inhibition of glucose reabsorption in the proximal tubules of the kidneys.[7] SGLT2 is responsible for 80-90% of glucose reabsorption in the proximal tubule and these drugs promote glucosuria which leads to improved glucose control by blocking SGLT2. SGLT2 inhibitors offer benefits including reductions in blood pressure, albuminuria and the progression of renal function decline.[8]

Dapagliflozin is an SGLT2 inhibitor historically approved only for patients with normal renal function (eGFR > 60 ml/min/1.73 m²).[9] The DERIVE study showed improved glycemic control and a favourable risk-benefit profile in T2DM patients with moderate CKD. Empagliflozin improves glycemic control and also offers cardiovascular benefits.[10] SGLT2 inhibitors have been associated with weight reduction, improved blood pressure and a lower risk of hypoglycemia compared to other antidiabetic agents. They also appear to reduce the urinary albumin-to-creatinine ratio indicating a potential protective effect on renal function.[11] SLGT2 inhibitors are glucose uric agents since the total reduction in reabsorption in glucose is directly proportional to GFR lesser amounts of glucose are directly filtered from the kidneys as the GFR falls and theoretically these drugs are of lesser efficacy in patients with reduced eGFR as compared to patients with diabetes and normal GFR. Therefore, safety and efficacy of these agents needs to be researched in CKD patients. SGLT2 inhibitors also have some other positive effects such as reduction in albuminurea and reduction in progressive decline of eGFR. Therefore, despite the reduced glucose uric effect in CKD, SGLT2 inhibitors can be considered in CKD patients.

CKD is a major complication of T2DM, still data on the efficacy of dapagliflozin in CKD stage 3A remain limited. SGLT2 inhibitors show renoprotective benefits but most studies focus on early CKD stages which leaves a gap in understanding their role in later stage disease progression. This study aims to assess the efficacy and safety of dapagliflozin in T2DM patients with CKD stage 3A. This provides crucial insights to guide clinical decision-making and optimize treatment strategies. The use of SGLT2 inhibitors in patients with compromised renal function, providing insights into their role in the management of diabetes and CKD.

Methodology

This study was approved by the Ethical Review Board of Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad. A randomized controlled trial was conducted at the Department of Nephrology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, from January 2022 to December 2022. The study was carried out after obtaining informed consent from all participants and was conducted over a period of 24 weeks following ethical approval from SZABMU (Ref. No. 1F-1/2015/ERB/SZABMU/441).

A total of 198 patients were initially randomized into two groups: 99 patients received dapagliflozin 10 mg (Group A), and 99 patients received a placebo (Group B). Ultimately, 79 patients in the treatment group and 83 patients in the control group completed the study, yielding a total of 162 participants.

The sample size was calculated using the WHO sample size calculator based on a significance level of 10%, a test power of 80%, and anticipated hypoglycemia rates of 38.8% for the drug group and 51.2% for the control group, as reported in the DERIVE trial.[10] Patients were selected using a non-probability consecutive sampling technique.

Inclusion criteria comprised adults aged 18 to 75 years with a history of type 2 diabetes mellitus (T2DM) for more than 12 months, inadequate glycemic control (HbA1c between 7.0% and 11.0%), a stable anti-diabetic treatment regimen, and chronic kidney disease stage 3A (eGFR 45–60 mL/min/1.73 m²). Exclusion criteria included a history of diabetic ketoacidosis, hyperosmolar non-ketotic coma, severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg), non-diabetic kidney disease, significant hepatic disease, ongoing treatment with SGLT2 inhibitors, GLP-1 analogues, or insulin, a history of urinary tract infections, unstable eGFR, and limb amputation.

Patients were randomized into two groups using the lottery method. Group A received dapagliflozin 10 mg/day, while Group B received placebo tablets; both were administered orally. Patients continued their existing glucose-lowering therapies and lifestyle modifications throughout the study period.

Baseline measurements and post-treatment evaluations at 24 weeks included HbA1c, serum urea, serum creatinine, and eGFR, calculated using the Modification of Diet in Renal Disease (MDRD) equation. Chronic kidney disease stages were classified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines.

Data were analyzed using SPSS version 21. Quantitative variables such as age, eGFR, and HbA1c levels were expressed as mean ± standard deviation. Qualitative variables, including gender, were presented as frequencies and percentages. Efficacy, in terms of changes in HbA1c and eGFR, was assessed using analysis of variance (ANOVA), while safety, measured by hypoglycemic events, was evaluated using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

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Results

Of the 162 participants, 55.7% (n=44) in Group A were male, while 66.2% (n=55) in Group B were male. The mean age was 52.9 years (± 8.5 SD) in Group A and 52.0 years (± 9.4 SD) in Group B. No significant age differences were found between the groups ($p > 0.05$). Table I

The mean estimated glomerular filtration rate (eGFR) in Group A was 52.14 ml/min/m² (± 4.8 SD), and the mean glycated haemoglobin (HbA1c) level was 8.2% (± 0.7 SD). The mean eGFR was 50.8 ml/min/m² (± 6.7 SD) in Group B, and the mean HbA1c level was 7.5% (± 0.2 SD). Table II

The efficacy of Dapagliflozin was assessed by the reduction in HbA1c levels. Group A showed a significant reduction in HbA1c levels compared to Group B after 6 months of treatment. The mean HbA1c level in Group A decreased from 8.2% (± 0.71 SD) to 7.7% (± 0.68 SD) with a mean reduction of 0.5%. Group B showed no significant change with mean HbA1c levels of 7.52% (± 0.38 SD) after treatment compared to 7.58% (± 0.72 SD) before the start of treatment. There was a significant reduction in HbA1c levels in Group A ($p = 0.002$). Table III

The safety of Dapagliflozin was evaluated by monitoring changes in eGFR and the incidence of hypoglycemic episodes. The mean eGFR was found not to be statistically significant but there was a slight decrease from 52.14 ml/min/m² (± 4.8 SD) to 51.27 ml/min/m² (± 5.8 SD) post-treatment in group A. The mean eGFR in group B decreased from 50.8 ml/min/m² (± 6.7 SD) to 47.6 ml/min/m² (± 6.0 SD) with a significant decline observed in the placebo group ($p < 0.000$). Table IV

Dapagliflozin was generally well-tolerated, with no serious adverse events reported. Hypoglycemic episodes were used as a safety marker. In Group A, 4 out of 79 patients (5%) experienced hypoglycemia, while in Group B, 5 out of 83 patients had hypoglycemic episodes. The incidence of hypoglycemia did not differ significantly between the treatment and placebo groups ($p = 0.79$), and the difference between males and females experiencing hypoglycemia was also not significant ($p = 0.80$).

Overall, the incidence of hypoglycemia was not higher in the treatment group as compared to the controlled study group and there was no significant difference between the number of hypoglycemic episodes in treatment versus placebo group p-value 0.79. Three male patients and six female's patient had an episode of hypoglycemia but this difference between male and female patients having hypoglycemic episodes was not significant with a p-value of 0.80.

Table I: Gender Distribution and Mean Age in Study Groups

	Group A (Dapagliflozin)	**Group B (Placebo)**	**Total**	**P values**
Male	44 (55.7%)	55 (66.2%)	99	0.17
Female	35 (44.3%)	28 (33.8%)	63	
Age Distribution	**Group A (Dapagliflozin)**	**Group B (Placebo)**	**Total**	
Mean Age (years)	52.9 ± 8.5	52.0 ± 9.4	-	0.52

Table II: Baseline Characteristics of Dapagliflozin and Placebo Groups

	Group A (Dapagliflozin)		
eGFR (ml/min/m²)	52.14 ± 4.8	50.8 ± 6.7	1.55
HbA1c (%)	8.2 ± 0.7	7.5 ± 0.2	0.002

Table III: HbA1c Reduction in Study Groups.

	Pre-Treatment HbA1c (%)	**Post-Treatment HbA1c (%)**	**Mean Reduction (%)**	**p-value**
Group A (Dapagliflozin)	8.2 ± 0.71	7.7 ± 0.68	0.5	0.002
Group B (Placebo)	7.58 ± 0.72	7.52 ± 0.38	0.06	0.19

Table IV: Changes in eGFR in Dapagliflozin and Placebo Groups.

eGFR Changes	**Pre-Treatment eGFR (ml/min/m²)**	**Post-Treatment eGFR (ml/min/m²)**	**Mean Change (ml/min/m²)**	**p-value**
Group A (Dapagliflozin)	52.14 ± 4.8	51.27 ± 5.8	-0.87	NS
Group B (Placebo)	50.8 ± 6.7	47.6 ± 6.0	-3.2	<0.000

Discussion

Diabetic kidney disease is the most significant cause of kidney disease around the world [12] and the results of the current study show that SGLT2 inhibitors reduce HbA1c levels significantly in diabetic populations and lead to reduction in HbA1c. SGLT2 inhibitors have also shown better cardiovascular outcomes in both study groups and they reduce the risk of CKD progression and death from end-stage renal disease regardless of blood sugar levels. SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by 0.6-1.2% in patients with intact eGFR. This aligns with the findings from the DERIVE study, where a reduction of 0.34% in HbA1c was observed in CKD 3a patients with eGFR between 45-30 ml/min/m2 treated with 10 mg of Dapagliflozin. While these results are significant, similar reductions in HbA1c can be achieved with other antidiabetic agents. However, the interest in SGLT2 inhibitors extends beyond their glycemic control, as these agents have shown beneficial effects on blood pressure, weight and outcomes related to chronic kidney disease and heart failure, making them increasingly preferred in clinical practice.

In the study by Arnott C et al., canagliflozin was associated with a lower risk of kidney and heart failure while a trial by Fitchett D et al., demonstrated similar cardiovascular benefits with Empagliflozin.[13,14] bothe these drugs belong the same class as Dapagliflozin i.e. SGLT2 inhibitors. The trial conducted by heerspink et al., highlighted the renoprotective effects of Dapagliflozin with a decreased rate of decline in eGFR and reduced risk of death from cardiac or renal failure. The trial included a normoglycemic population, emphasizing the potential benefits of SGLT2 inhibitors beyond glycemic control.[15] The mechanism of action of SGLT2 inhibitors involves reducing glucose reabsorption in the proximal convoluted tubule. Studies have shown that SGLT2 inhibitors still provide modest reductions in HbA1c in CKD patients. While other medications might achieve similar HbA1c reductions in CKD populations, the additional benefits of SGLT2 inhibitors, such as blood pressure and weight reduction, as well as cardiovascular protection, make them a compelling choice in clinical practice.[7]

Dapagliflozin was validated as a safe and efficacious treatment in CKD 3a patients in the current study with no significant increase in hypoglycemic episodes and no significant decline in eGFR. The mean reduction in HbA1c was 0.5% after 24 weeks of therapy in patients with a baseline HbA1c of over 7% and eGFR between 45-60 ml/min/m2. These results are consistent with the DERIVE study, which reported a 0.34% reduction in HbA1c under similar conditions.[10] Kohan et al. demonstrated a -0.44% mean reduction in eGFR in a related study.[16] A 2019 study by Lin et al., found a reduction in HbA1c from 8.890% to 7.994% after 12 weeks of SGLT2 therapy.[17]

Other SGLT2 inhibitors, such as Canagliflozin and Empagliflozin, have also shown similar efficacy in reducing HbA1c in CKD populations, with reductions of -0.4% and -0.6%, respectively. As previously mentioned, the efficacy of Dapagliflozin is reduced in CKD due to the lower eGFR, which limits glucose filtration. Studies in patients with normal renal function have demonstrated greater HbA1c reductions, further supporting this observation. Clifford et al. reported a -0.9% reduction in HbA1c in diabetic patients without renal dysfunction when 10 mg of Dapagliflozin was administered daily, and John P. et al. observed a -0.78% reduction under similar conditions.[18,19]

Other medications such as Sitagliptin have also been used in CKD patients with similar efficacy in reducing HbA1c. In a randomized controlled trial, Chan et al. demonstrated a -0.7% reduction in HbA1c using Sitagliptin in CKD patients.[20] The additional cardiovascular and blood pressure-lowering benefits of SGLT2 inhibitors make them the preferred choice in treating diabetes in CKD patients.

In the current study, the number of hypoglycemic episodes and changes in eGFR were primary endpoints for evaluating safety. Only four out of seventy-eight patients in the treatment group experienced hypoglycemia after 24 weeks of therapy, which was not significantly different from the placebo group. These results align with the DERIVE study, where Dapagliflozin did not lead to a higher incidence of hypoglycemia.[10] Given the overall prevalence of hypoglycemia in diabetic patients receiving standard care, particularly insulin, the occurrence of hypoglycemia in only 5% of the treatment group highlights the relative safety of Dapagliflozin in this regard.

In this study the mean pre-treatment eGFR in the treatment group was 52.14 ml/min/m2 ± 4.8 SD, and the post-treatment eGFR was 51.274 ml/min/m2 ± 5.8 SD. Dapagliflozin did not significantly impact renal function because the mean change in eGFR was insignificant. In contrast, the placebo group showed a mean decrease in eGFR of 4 ml/min/m2 after 24 weeks, further supporting the renoprotective effects of Dapagliflozin. These findings are consistent with the DAPA-CKD trial, which demonstrated a greater than 50% reduction in the composite risk of eGFR decline in CKD patients, regardless of glycemic status.[15] A study by Suguyama et al. reported comparable renoprotective effects with Dapagliflozin.[21]

The results of this study support the conclusion that Dapagliflozin is safe in CKD patients. Its efficacy in CKD is somewhat reduced due to lower eGFR results in the current study results but the renoprotective, cardio protective properties and the blood pressure-lowering effects make it viable for treating diabetes in CKD patients. This study fills a gap in the literature by specifically evaluating the safety and efficacy of Dapagliflozin in CKD 3a patients, contributing valuable insights to the ongoing research in this field.

Conclusion

Dapagliflozin was found to be efficacious in reducing HBA1C by -0.5% along with efficacy. Dapagliflozin was also found to be safe and not associated with an elevated risk of developing hypoglycemia and there was no significant decrease in eGFR after 24 weeks of therapy.

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