ORIGINAL ARTICLE

Efficacy of Empagliflozin in Slowing the Progression of Renal Disease in Patients with Type 2 Diabetes: Single-Blind Interventional Study with Placebo Control at Tertiary Care Setting Quetta

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ABSTRACT

Objective: To assess the role of SGLT2 Inhibitor, Empagliflozin, in slowing renal disease progression in type 2 diabetics.

Study Design: Single-blind interventional study with placebo control.

Place and Duration of Study: The study was carried out at the Department of Nephrology, Combined Military Hospital (CMH), Quetta, Pakistan from July 2023 to July 2024.

Methods: This was an experimental study with placebo controlinvolving 100 type 2 diabetics (N=100), who were assigned to receive either Empagliflozin (10 mg OD) or a placebo. Estimated glomerular filtration rate (eGFR) by (CKD-EPI Formula), HbA1C levels, and Urine Protein Creatinine Ratio (UPCR) were measured at 0, 3, and 6 months. Improvement in GFR and reduction in proteinuria & HbA1C levels were taken as primary objectives. Three mixed-design analyses of variance over time (baseline, 3 months, 6 months) conducted for significance.

Results: Average age was 57.44 ± 10.48 years. The treatment group had 47 patients, and the placebo group had 53 patients. The treatment group showed a lesser reduction in mean eGFR (70.94mL/min to 68.56mL/min) than the placebo group (69.60mL/min to 62.11mL/min). The treatment group showed a greater decrease in HbA1c levels (8.36% to 7.36%) than the placebo (8.30% to 8.01%). Proteinuria was reduced in the treatment group (2.51 g/day to 1.28 g/day) compared to an increase in the placebo group (2.66 g/day to 3.17 g/day). All findings were statistically significant ($P < 0.05$).

Conclusion: In type 2 diabetics, addition of empagliflozin to standardized care resulted in a greater reduction in proteinuria, greater reduction in HbA1c levels, and lesser decline in eGFR, signifying the beneficial effects of the drug on glycemic control and prevention of renal deterioration.

Keywords: *Chronic, Diabetes Mellitus Type 2, Diabetic Nephropathies, Empagliflozin, Renal Insufficiency, Sodium-Glucose Transporter 2 Inhibitors.*

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Introduction

Chronic kidney disease (CKD) is among the most severe complications of type 2 diabetes mellitus (T2DM), and it is estimated that up to 40% of patients worldwide will suffer from CKD. CKD is an important factor of end-stage renal disease (ESRD) and is a major risk factor for cardiovascular disease and death.[1,2] Despite advances in treatment, controlling CKD progression in patients with T2DM remains challenging. Traditional remedy modalities, including lowering blood glucose and the inhibition

of the renin-angiotensin-aldosterone system (RAAS), commonly do not sufficiently shield against the degeneration of kidney performance.[3,4] Therefore, there is a growing interest in new agents that could provide glycemic control and renal protection at the same time.

Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor that has demonstrated cardioprotective effects, has also appeared to have renal benefits independent of blood glycemic control. Originally approved to lower blood glucose by promoting the urinary excretion of glucose, empagliflozin has also been shown to slow CKD progression in patients with T2DM.[5]

The landmark EMPA-REG OUTCOME trial and other studies have highlighted its ability to slow the progression of estimated glomerular filtration rate (eGFR) loss, decrease urinary albumin excretion, and reduce the risk of developing ESRD.[6,7]

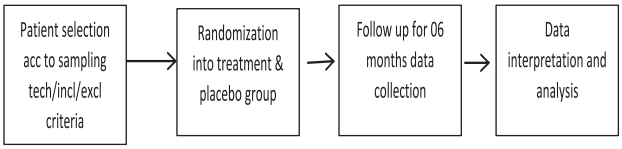
It is thought that empagliflozin's renal protective properties are mediated by multiple mechanisms, including reduced intraglomerular pressure, reduced renal inflammatory burden, and improved hemodynamic stability.[8,9] Additionally, the prevention of sodium reabsorption is associated with improved tubular oxygenation and reduced oxidative stress.[10]

The aim of our study is to further evaluate the efficacy of empagliflozin in slowing renal disease progression among T2DM patients by comparing changes in eGFR and HbA1c between empagliflozin and placebo over a 12-month period. This, together with the accumulating evidence on the role of SGLT2 inhibitors in the management of diabetic kidney disease, will add further weight to the case for such drugs as a cornerstone of the management of diabetes and its complications.

Methods

The study was conducted at the Department of Nephrology, Combined Military Hospital (CMH) Quetta, Pakistan from July 2023 to July 2024 after taking permission from the Institutional Ethical Review Board of the hospital vide letter no: CMH QTA- IERB/16/2023, dated: 16th June 2023. One hundred subjects (N=100), both males and females, over 35 years of age, with type 2 diabetes and eGFR ≥30 ml/min/1.73 m² (CKD-EPI Formula) were selected from Nephrology OPD, Combined Military Hospital, Quetta, by a non-probability consecutive sampling technique. Patients with other proteinuric diseases, non-compliant to medications, unwilling/unable to follow up, and concomitant endocrine disorders were excluded from the study. The patients were then randomly assigned to either the treatment or the placebo group using a computer-generated random sequence generator. Single blinding was done at this point. The treatment group was given Tab Empagliflozin 10 mg once daily, along with anti-diabetic plus supportive treatment (including ACEIs/ARBS). The placebo group received anti-diabetic treatment plus supportive treatment only. Baseline eGFR, HbA1c, and 24 hours urine protein levels were taken and documented on a proforma. The same parameters were also measured at 3 and 6 months. The primary outcomes were improvement in eGFR, decrease in HbA1C levels, reduction in 24-hour urine protein levels, and reduction in 24-hour urine protein excretion.

After the data was collected, it was compiled in a Microsoft Excel worksheet and later exported to SPSS version 26. Descriptive statistics were used to estimate means, frequencies, and standard deviations. Three mixed-design ANOVAs were used to investigate the effectiveness of treatment (empagliflozin vs. placebo) over time (baseline, 3 months, 6 months) on the dependent variables of eGFR, proteinuria, and HbA1c. Time was the within-subjects factor, and treatment was the between-subjects factor. Mauchly's test of sphericity was performed to analyze the postulates of sphericity, and where dishonored, Greenhouse-Geisser corrections were used. Partial eta squared (η^2) was stated as a measure of effect size. Separate analyses were performed to allow for an independent assessment of each outcome. To account for numerous comparisons, the Bonferroni modification was applied, setting the threshold at α=0.0167.



Results

The study included 100 participants of which 47 belonged to Empagliflozin group and 53 to placebo group. The average age of the patients was 57.44 ± 10.48 in between 40—75 years. The empagliflozin group had average age of 58.21 ± 10.07 years, while placebo group had average age of 53 ± 10.88 years. The sample comprised 53 males (53%) and 47 females (47%). Gender distribution was consistent across treatment groups, with 56% males and 44% females in both the empagliflozin and placebo groups.

At baseline, the Empagliflozin group had an eGFR value of 70.94 ± 12.12, while the placebo group had 69.60 ± 12.69. After 3 months, the Empagliflozin group showed a slight decrease to 69.72 ± 12.08, whereas the placebo group decreased to 65.92 ± 12.40. At 6 months, the Empagliflozin group's eGFR was 68.56 ± 11.98, and the placebo group was 62.11 ± 12.83.

Baseline HbA1c was 8.36 ± 0.70% (Empagliflozin) and 8.30 ± 0.75% (placebo). At three months of treatment, HbA1c was reduced to 7.80 ± 0.69% in the Empagliflozin group vs. 8.14 ± 0.75% in the placebo group. At six months, the Empagliflozin group declined further to 7.36 ± 0.66%, whereas the placebo group only achieved a mild reduction at 8.01 ± 0.74%.

Patients had higher proteinuria: 2.51 ± 0.51 g/day in the Empagliflozin group and 2.66 ± 0.52 g/ day in the placebo group. At three months, the Empagliflozin group showed a reduction to 1.55 ± 0.50 g/day, whereas levels remained steady in the placebo group at 2.66 ± 0.52 g/day.

At 6 months, proteinuria was further reduced in the Empagliflozin group by −0.45 g/day [1.28 ± 0.62 g/day, N=35; Empagliflozin group at 6 months] compared to the placebo group, which reached a significant increase of 3.17 ± 0.55 g/day. (Table 1).

The impact of time and treatment group

Table 1: Descriptive Statistics of Estimated Glomerular Filtration Rate, Proteinuria, and Glycated Hemoglobin Across Time Points and Treatment Groups

Variable	Time Point	Empagliflozin (M ± SD)	Placebo (M ± SD)
Estimated glomerular filtration rate (mL/min/1.73 m²)	Baseline	70.94 ± 12.12	69.60 ± 12.69
	3 months	69.72 ± 12.08	65.92 ± 12.40
	6 months	68.56 ± 11.98	62.11 ± 12.83
Glycated hemoglobin (%)	Baseline	8.36 ± 0.70	8.30 ± 0.75
	3 months	7.80 ± 0.69	8.14 ± 0.75
	6 months	7.36 ± 0.66	8.01 ± 0.74
Proteinuria (g/day)	Baseline	2.51 ± 0.51	2.66 ± 0.52
	3 months	1.55 ± 0.50	2.66 ± 0.52
	6 months	1.28 ± 0.62	3.17 ± 0.55

M ± SD, mean ± standard deviation

Table 2: Results of the Mixed Factorial Analysis of Variance for Estimated Glomerular Filtration Rate Across Time Points and Treatment Groups

Source	SS	df	MS	F	Partial η²	*P* value
Time	1212.569	1.68	721.537	816.35	0.893	<0.001
Treatment Group	1116.684	1	1116.684	2.44	0.024	0.121
Time × Treatment Group	324.916	1.681	193.341	218.74	0.691	<0.001

Note: ANOVA, analysis of variance; SS, sum of squares; df, degrees of freedom; MS, mean square; p , probability

Table 3: Results of the Mixed Factorial Analysis of Variance for Proteinuria Across Time Points and Treatment Groups

Source	SS	df	MS	F	Partial η^2	*P* value
Time	12.421	1.131	10.982	78.99	0.446	<0.001
Treatment Group	82.397	1	82.397	117.71	0.545	<0.001
Time × Treatment Group	37.982	1.131	33.581	241.52	0.711	<0.001

Note: ANOVA, analysis of variance; SS, sum of squares; df, degrees of freedom; MS, mean square; p , probability

Table 4: Results of the Mixed Factorial Analysis of Variance for Glycated Hemoglobin Across Time Points and Treatment Groups

Source	SS	df	MS	F	*P value*	Partial η^2
Time	20.804	1.449	14.362	811.16	<0.001	0.892
Treatment Group	7.23	1	7.23	4.744	0.032	0.046
Time × Treatment Group	6.329	1.449	4.369	246.77	<0.001	0.716

Note: ANOVA, analysis of variance; SS, sum of squares; df, degrees of freedom; MS, mean square; P, probability

(empagliflozin vs. placebo) on eGFR was assessed using a mixed-design ANOVA. The effect of time was significant, F (1.68,164.7) = 816.35, $P<0.05$, η = 0.893, indicating that eGFR values changed significantly over the measured time points (baseline, 3 months, and 6 months).

The prominent effect of treatment group was not significant, F (1, 98) = 2.44, $P = 0.121$, η = 0.024, suggesting that no significant change in overall eGFR levels in the empagliflozin and placebo groups.

Nevertheless, comparing the time and treatment groups F (1.68, 164.7) = 218.74, $P < 0.05$, η = 0.691, indicating that the pattern of change in eGFR over time was significantly different between the two groups. (Table 2).

A mixed-design ANOVA was led to evaluate the effect of the time & treatment group (empagliflozin vs. placebo) on proteinuria. The prominent effect of time was important, F (1.13, 110) = 78.99, $P < 0.05$, η = 0.446, indicating that proteinuria levels differed significantly across time points. The prominent effect of treatment group was worthy, F (1, 98) = 117.71, $P <$ 0.05, η = 0.546, showing that the proteinuria levels were known to be reduced in the empagliflozin group in contrast to the placebo group.

Additionally, there was a significant interaction between time and treatment group, F (1.13,110) = 241.52, $P<0.05$, η=0.711. This result shows that the difference in proteinuria levels on time modified significantly in the treatment groups. (Table 3).

The impact of time and treatment group (empagliflozin vs. placebo) on HbA1c levels was assessed using a combined-design ANOVA. The critical effect of time was demonstrated by F (1.45, 142) = 811.16, $P < 0.05$, η = 0.892, indicating that HbA1c levels changed significantly over the measured time points (baseline, 3 months, and 6 months).

The prominent effect of treatment group was shown in F (1, 98) = 4.74, $P = 0.032$, η = 0.046, suggesting the HbA1c levels were significantly reduced in the empagliflozin group in contrast to the placebo group.

Additionally, the interaction between time and treatment group was significant, F (1.45,142) = 246.77, $P<0.05$, η=0.716. This suggests that there were notable differences in the treatment groups' changes in HbA1c levels over time. (Table 4).

Discussion

These results of our investigation demonstrate that the empagliflozin portrays reduced progression of renal disease in the population with T2DM, as evidenced by a slower rate of decline in eGFR in relation to placebo. Indeed, these findings are consistent with prior research that focused on the renoprotective effect of SGLT2 inhibitors. Empagliflozin, a SGLT2 inhibitor, has emerged as a critical agent in the prevention of progressive kidney disease in people with T2DM. The current discussion refers to insights gained from recently generated data, underscoring the drug's broad-spectrum efficacy, safety, and mechanism of action. Background: Empagliflozin substantially reduces the

deterioration of eGFR and albuminuria in patients with DKD. A randomized trial by Nielsen SF et al. showed that empagliflozin decreases renal blood flow, thereby interrupting hyperfiltration, a central event in the pathogenesis of DKD.[11] This finding aligns with the work of Sadiq H et al., who also noted improved kidney outcomes independent of initial renal function.[12] The cardiovascular benefits of empagliflozin are essential for its nephroprotective effects. Li P et al. emphasized that the reduction of heart failure hospitalizations from this class of agents subsequently decreases renal stress.[13] Likewise, Feola M et al. showed improvements in measures of arterial stiffness and cardiovascular risk factors among patients treated with empagliflozin.[14] Unlike other SGLT2 inhibitors, empagliflozin has often demonstrated superior renal and cardiovascular outcomes. A cohort study by Hussain et al. compared empagliflozin with dapagliflozin, revealing that the former had lower rates of significant adverse renal and cardiovascular events.[15] These results advocate for its preferred use in patients facing both cardiovascular and renal risks. Although the overall safety profile of empagliflozin is favorable, adverse effects like euglycemic diabetic ketoacidosis (DKA) remain rare but notable. Toan AT et al. discussed these risks, emphasizing the importance of patient selection and monitoring.[16] These findings are corroborated by Milder TY et al. who reported higher discontinuation rates in patients hospitalized for heart failure but noted that this could be mitigated with better patient education.[17] Empagliflozin reduces intraglomerular pressure via tubuloglomerular feedback and alleviates oxidative stress, contributing to its renoprotective effects. Sato H et al. explored these mechanisms, demonstrating that the drug's action extends beyond glucose lowering to encompass anti-inflammatory and antifibrotic pathways.[18] Economic evaluations indicate that empagliflozin's cost-effective for managing DKD. Wales highlighted its long-term benefits, noting reduced healthcare costs due to fewer hospitalizations and delayed progression to end-stage renal disease.[19] Empagliflozin's role in renal transplantation is an emerging area of research. Tsiakas et al. study provided preliminary data on its safety and efficacy in kidney transplant recipients.[20] Further ongoing trials will help clarify its potential in wider patient groups, including those who do not have diabetes but are at risk of chronic kidney disease. Empagliflozin represents a new strategy in DKD management in T2DM that offers dual benefits by preserving cardiac and renal health. Future studies should focus on expanding its use across diverse populations and on refining patient outcomes through individualized therapy strategies.

Conclusion

Empagliflozin is of key importance in preventing the progression of kidney injury in patients with T2DM. Its main effects are to reduce albumin levels, preserve eGFR, and delay ESRD. Its renal protective effects are not limited to hypoglycemia but also involve vasodilatory and anti-inflammatory mechanisms. In addition, the cardiorenal benefits of empagliflozin, including reduced risk for heart failure, subsequently also translate into improvements in renal outcomes. These data support the role of empagliflozin as a cornerstone treatment for T2DM patients at risk of kidney complications. Future studies should explore the long-term benefits of this approach and broader applicability for other populations at high risk, including those without diabetes but with high risks for kidney dysfunctions.

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Author Contributions

ZK: Conception and design of the work
AA: Writing the original draft, proofreading, and approval for final submission
SJ: Data acquisition, curation, and statistical analysis
MUI: Revising, editing, and supervising for intellectual content
NF: Validation of data, interpretation, and write-up of results
AI: Manuscript writing for methodology design and investigation