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SAFETY AND EFFICACY OF SGLT2 INHIBITORS IN RENAL TRANSPLANT RECIPIENTS

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Abstract

Objective: To evaluate the safety profile and effectiveness of Empagliflozin (SGLT 2 inhibitor) in treating PTDM (post-transplant diabetes mellitus) specifically in renal transplant recipients. Methods: This single-center randomized case-control trial was conducted in the Armed Forces Institute of Urology, Rawalpindi, from January 2025 to May 2025. Patients who underwent renal transplantation and who developed PTDM were enrolled. Group P: patients received a placebo drug daily for 20 weeks, and Group E patients received Empagliflozin for 20 weeks daily. The patients were called for regular follow-up at weeks 5, 10, 15, and 20. Fasting blood sugar (FBS), and HbA1c were noted before starting the treatment, and at each follow-up. Results: The average age of participants in Group E was 35.5±6.2 years while Group P had an average age of 34.9±7.1 years (p-value 0.75). The duration after transplantation was similar as well, with Group E reporting an average of 3.2(±1.8) years and Group P reporting 3.4 (±1.7) years (p-value 0.68). There was no significant difference in baseline HbA1c, FBS and BMI of participants. However, by week 20, FBS levels in Group E had decreased significantly to 128±6 mg/dL, compared to 137±8 mg/dL in Group P (p<0.0001). HbA1c in Group E had dropped to 6.6±0.30%, while Group P had increased to 6.9±0.31% (p=0.001). Hemoglobin levels also showed increase in group E. Conclusion: The use of Empagliflozin significantly improves glycemic control and helps in weight reduction in patients with PTDM in renal transplant recipients.

INTRODUCTION

Kidney transplantation represents the optimal treatment option for individuals suffering from end-stage kidney disease (ESKD). This surgical procedure not only extends lifespan but also significantly enhances the quality of life when compared to traditional renal replacement therapies. However, despite these benefits, kidney transplantation can lead to various complications for recipients. Notable adverse effects include an increased risk of infections, risks of rejection, the potential development of malignancies, cardiovascular issues, and the onset of post-transplant diabetes mellitus.[1, 2]

Hyperglycemia frequently occurs following kidney transplantation and poses a risk for developing post-transplantation diabetes mellitus (PTDM). PTDM refers to the onset of diabetes mellitus that is

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identified after the transplantation, regardless of whether it was previously undiagnosed. It is specifically diagnosed in patients who are clinically stable and do not experience temporary hyperglycemia after the procedure.[3,] PTDM refers to the persistent hyperglycemia that lasts for at least six weeks following transplantation.[4] The prevalence of PTDM in patients receiving kidney transplants from living or deceased donors varies between 15% and 30%, highlighting its significance as a health concern that has drawn considerable attention and research in recent years.[5, 6] Sodium-glucose co-transporter 2 (SGLT-2) inhibitors represent a new class of oral medications that lower blood glucose levels by blocking the reabsorption of glucose in the proximal tubule of the kidneys, leading to increased glucose excretion. Although SGLT-2 inhibitors have been found to be effective in managing blood sugar, their impact on reducing hemoglobin A1C (HbA1c) levels is considered modest, with reductions typically ranging from 0.4% to 1.1%.[7, 8] This mechanism of action is distinct because it operates independently of insulin sensitivity and beta-cell function, meaning these medications are less likely to cause hypoglycemic events. Notably, Empagliflozin, one of the SGLT-2 inhibitors, has not only demonstrated efficacy in improving glycemic control in patients with type 2 diabetes but has also shown promise in reducing the risk of cardiovascular and renal complications among individuals who are at an elevated risk for such events.[9, 10] If confirmed to be both safe and effective, the inhibition of SGLT-2 could offer significant long-term benefits for individuals dealing with post-transplant diabetes mellitus (PTDM), potentially enhancing both patient and graft survival rates. The purpose of this study is to evaluate the safety and effectiveness of Empagliflozin in treating PTDM, specifically in renal transplant patients.

METHODS:

This single-center randomized case-control trial was conducted in the Armed Forces Institute of Urology, Rawalpindi, from January 2025 to June 2025. Patients who underwent renal transplantation 1year post-transplant, who developed PTDM, who have stable renal functions and stable immunosuppression, were enrolled. The criteria established for identifying PTDM included renal transplant recipients who did not have diabetes before their surgery but experienced persistent hyperglycemia for at least one year following transplantation. We identified these patients through oral glucose tolerance tests (OGTTs) and/or HbA1c measurements collected both prior to transplantation and during a comprehensive evaluation conducted one-year post-transplant at our facility. While patients with UTI and having signs of transplant rejection were excluded. In total, we enrolled 50 patients, who were then randomly divided into two groups using a simple random sampling method (envelope technique). This division was executed by an individual who had no direct involvement in the study's practical aspects.

Group P patients received a placebo drug daily for 20 weeks, and Group E patients received Empagliflozin for 20 weeks daily. The patients were called for regular follow-up at weeks 5, 10, 15 and 20. Fasting blood sugar (FBS), and HbA1c were noted before starting the treatment, and at each follow-up.

Participants were advised to maintain their usual dietary and exercise routines throughout the duration of the study. Their medications were to remain the same unless it was necessary to reduce the dosage of glucose-lowering agents. To verify adherence to the protocol, capsule counts were conducted at the 8-week and 20-week intervals. Safety assessments were carried out at weeks 5, 10, 15 and 20, which included a physical examination, routine blood tests for safety, and trough level measurements for immunosuppressive drugs. Additionally, patients participated in focused interviews to detect any adverse effects, and all reported incidents were carefully logged.

Data was analyzed using SPSS v. 25. An independent sample was applied to compare FBS and HbA1c at baseline and at the final 20th week follow-up, by considering p-value ≤0.05 as significant.

RESULTS:

The baseline characteristics revealed several key demographics. The average age of participants in Group E was 35.5±6.2 years, while Group P had an average age of 34.9±7.1 years (p-value 0.75). The duration after transplantation was also similar, with Group E reporting an average of 3.2 (±1.8) years and Group P reporting 3.4 (±1.7) years (p-value 0.68). In terms of gender distribution, 76% (19 individuals) of

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Group E were male compared to 80% (20 individuals) in Group P (p-value 0.11). The immunosuppressive therapy utilized in both groups showed similarities as well: 92% (23 individuals) of both groups were on Prednisolone, with a p-value of 1.0. Tacrolimus was used by 80% (20 individuals) in Group E and 76% (19 individuals) in Group P, leading to a p-value of 0.73. Mycophenolate was administered to 88% (22 individuals) in Group E and 92% (23 individuals) in Group P, resulting in a p-value of 0.63. Cyclosporin was noted in 16% (4 individuals) of each group, showing no significant difference (p-value of 1.0). For antidiabetic treatments, DPP-4 inhibitors were used by 48% of Group E and 44% of Group P (p=0.94), while sulfonylureas, metformin, and insulin were also similarly distributed across the two groups. Overall, the baseline characteristics of the groups showed no significant differences across the examined variables (Table 1).

Comparing clinical outcomes between Group E and Group P revealed several key findings. At the start, fasting blood sugar (FBS) levels were 145±8 mg/dL in Group E and 149±10 mg/dL in Group P (p=0.12). However, by week 20, FBS levels in Group E had decreased significantly to 128±6 mg/dL, compared to 137±8 mg/dL in Group P (p<0.0001). Baseline HbA1c levels were similar, at 6.8±0.42% for Group E and 6.7±0.25% for Group P (p=0.31), but by week 20, HbA1c in Group E had dropped to 6.6±0.30%, while Group P had increased to 6.9±0.31% (p=0.001). Body Mass Index (BMI) was also comparable at baseline, with Group E at 28.5±3.4 Kg/m² and Group P at 27.8±3.1 Kg/m² (p=0.45), showing no significant changes by week 20 (27.9±3.2 Kg/m² for Group E vs. 28.0±3.5 Kg/m² for Group P, p=0.91). Uric acid levels showed a significant difference at baseline (405±27 µmol/L for Group E and 387±23 µmol/L for Group P, p-value 0.01) and at week 20 (320±23 µmol/L for Group E compared to 382±22 µmol/L for Group P, p=0.0001). Hemoglobin levels were similar at baseline (13.1±1.4 g/dL for Group E and 13.3±1.3 g/dL for Group P, p=0.60) and remained consistent by week 20 (13.6±1.2 g/dL for Group E and 13.5±1.0 g/dL for Group P, p-value 0.75) [Table 2]. Regarding safety, one patient (4.0%) in group E developed a UTI, while three patients (12.0%) in group P experienced other treatment-related complications.

Table 1. Baseline Characteristics.

	Group E (N=25)	Group P (N=25)	p-value
Age (Years)	35.5±6.2	34.9±7.1	0.75
Duration after Transplantation (Years)	3.2±1.8	3.4±1.7	0.68
Male Gender (%)	19 (76.0%)	20 (80.0%)	0.11
Immunosuppressive Therapy (%)			
Prednisolone	23 (92.0%)	23 (92.0%)	1.0
Tacrolimus	20 (80.0%)	19 (76%)	0.73
Mycophenolate	22 (88.0%)	23 (92.0%)	0.63
Cyclosporin	04 (16.0%)	04 (16.0%)	1.0
Antidiabetic treatment (%)			
DPP-4 inhibitors	12 (48.0%)	11 (44.0%)	0.94
Sulfonylurea	3 (12.0%)	4 (16.0%)	
Metformin	5 (20.0%)	4 (16.0%)	
Insulin	5 (20.0%)	6 (24.0%)	

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Table 2. Comparison of Clinical Outcomes.

	Group E (N=25)	Group P (N=25)	p-value
Baseline FBS Levels (mg/dL)	145±8	149±10	0.12
FBS Levels at 20th week (mg/dL)	128±6	137±8	<0.0001
Baseline HbA1c Levels (%)	6.8±0.42	6.7±0.25	0.31
HbA1c Levels at 20th week (%)	6.6±0.30	6.9±0.31	0.001
BMI Baseline (Kg/m^2)	28.5±3.4	27.8±3.1	0.45
BMI at 20th week (Kg/m^2)	27.9±3.2	28.0±3.5	0.91
Baseline Uric Acid (µmol/L)	405±27	387±23	0.01
Uric Acid at 20th week (µmol/L)	320±23	382±22	0.0001
Baseline Hemoglobin (g/dL)	13.1±1.4	13.3±1.3	0.60
Hemoglobin at 20th week (g/dL)	13.6±1.2	13.5±1.0	0.75

DISCUSSION:

Diabetes mellitus following kidney transplantation poses significant challenges in managing patients who have undergone this procedure. Post-transplant diabetes mellitus (PTDM) can impact both patient well-being and the survival of the transplanted kidney.[11, 12] Various approaches have been employed to address this issue, considering individual patient needs. One effective class of medications, SGLT-2 inhibitors, aids in the renal elimination of glucose and helps to modestly reduce elevated blood sugar levels in individuals diagnosed with type 2 diabetes.[13]

In our study, we determined the role of Empagliflozin for managing PTDM after renal transplantation. We found significant beneficial effects of Empagliflozin in terms of reduction in FBS and HbA1c levels at 20 weeks follow-up.

Recent research has explored the effects of empagliflozin in a randomized controlled trial involving kidney transplant recipients. The study included 44 participants, equally divided into two groups: one receiving empagliflozin and the other a placebo, with a total of 34 males involved. Results showed that HbA1c levels decreased significantly in the empagliflozin group compared to the placebo. The extent of glucose reduction was influenced by the estimated glomerular filtration rate (eGFR) as well as the initial HbA1c levels. Participants treated with empagliflozin also experienced a notable decrease in body weight compared to those in the placebo group. However, there were no significant changes in blood pressure and no meaningful differences observed between the two groups concerning adverse events, immunosuppressive drug levels, or eGFR measurements.[14]

The EMPA-REG OUTCOME trial evaluated the effects of empagliflozin in patients with Type 2 Diabetes Mellitus who also had established cardiovascular diseases. A total of 7,028 participants, with an average HbA1c level around 8%, were randomly assigned to receive either empagliflozin or a placebo. Most of these patients were on metformin to manage their blood glucose levels, and notably, about 48% from both groups were also using insulin. After three years of treatment, the results indicated that the primary composite outcome, which included death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, affected fewer patients on empagliflozin compared to those on placebo (10.5% versus 12.1%; pooled analysis hazard ratio [HR] 0.86; 95% confidence interval [CI], 0.74-0.99). This outcome was significantly influenced by a notable reduction in the risk of cardiovascular-related deaths, which occurred in 3.7% of the empagliflozin group versus 5.9% in the placebo group (HR 0.62; 95% CI, 0.49-0.77). Furthermore, hospitalization rates for heart failure were also lower among patients receiving empagliflozin, at 2.7% compared to 4.1% in those receiving placebo.[15]

A recent meta-analysis by Chewcharat et al. including 8 studies reported that the use of SGLT-2 inhibitors is associated with significant reduction in HbA1c levels and body weight in comparison to conventional antidiabetic treatment.[16]

The use of SGLT2 inhibitors enhances the excretion of glucose in urine, which leads to a reduction in blood glucose concentrations. This decrease in

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glucose levels subsequently results in a decline in insulin secretion while glucagon secretion is elevated, causing the release of free fatty acids (FFA) primarily from adipose tissues. In the liver, these fatty acids are transformed into ketones. The glycosuria induced by SGLT2 inhibitors decreases carbohydrate availability, prompting a shift in energy metabolism from glucose to fat oxidation. Additionally, the increase in glucagon levels encourages ketogenesis. Ketones are recognized as potent energy sources. These findings suggest that treatment with SGLT2 inhibitors could enhance the breakdown of stored fat, transitioning the body toward a more significant reliance on fat as a source of energy.[17-19]

The study is limited by small sample size and shorter follow-up duration. More studies are needed to evaluate the role of Empagliflozin for treating PTDM in renal transplant recipients.

CONCLUSION:

The use of Empagliflozin significantly improves glycemic control and helps in weight reduction in patients with PTDM in renal transplant recipients. Therefore, Empagliflozin can be administered to patients with PTDM to improve glycemic control.

REFERENCES

1. Kim PY, Shoghi A, Fananapazir G. Renal Transplantation: Immediate and Late Complications. Radiologic clinics of North America. 2023;61(5):809-20.
2. Pham NT, Cruz D, Madera-Marin L, Ravender R, Garcia P. Diabetic Kidney Disease in Post-Kidney Transplant Patients. Journal of clinical medicine. 2024;13(3).
3. Iqbal A, Zhou K, Kashyap SR, Lansang MC. Early Post-Renal Transplant Hyperglycemia. The Journal of clinical endocrinology and metabolism. 2022;107(2):549-62.
4. Classification and Diagnosis of Diabetes. Standards of medical care in diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15-s33.
5. Rossi MR, Mazzali M, de Sousa MV. Post-transplant diabetes mellitus: risk factors and outcomes in a 5-year follow-up. Frontiers in clinical diabetes and healthcare. 2024;5:1336896.
6. Alanazi NF, Almutairi M, Aldohayan L, AlShareef A, Ghallab B, Altamimi A. The incidence and risk factors of post-transplant diabetes mellitus in living donor kidney transplantation patients: a retrospective study. BMC nephrology. 2024;25(1):394.
7. Daniele G, Solis-Herrera C, Dardano A, Mari A, Tura A, Giusti L, et al. Increase in endogenous glucose production with SGLT2 inhibition is attenuated in individuals who underwent kidney transplantation and bilateral native nephrectomy. Diabetologia. 2020;63(11):2423-33.
8. DeFronzo RA. SGLT2 inhibitors: cardiorenal metabolic drugs for the ages. The Journal of clinical investigation. 2024;134(5).
9. Cai C, Guo Z, Chang X, Li Z, Wu F, He J, et al. Empagliflozin attenuates cardiac microvascular ischemia/reperfusion through activating the AMPKα1/ULK1/FUNDC1/mitophagy pathway. Redox biology. 2022;52:102288.
10. Yang W, Li X, He L, Zhu S, Lai S, Zhang X, et al. Empagliflozin improves renal ischemia-reperfusion injury by reducing inflammation and enhancing mitochondrial fusion through AMPK-OPA1 pathway promotion. Cellular & molecular biology letters. 2023;28(1):42.
11. Shivaswamy V, Boerner B, Larsen J. Post-Transplant Diabetes Mellitus: Causes, Treatment, and Impact on Outcomes. Endocrine reviews. 2016;37(1):37-61.
12. Munoz Pena JM, Cusi K. Posttransplant Diabetes Mellitus: Recent Developments in Pharmacological Management of Hyperglycemia. The Journal of clinical endocrinology and metabolism. 2023;109(1):e1-e11.
13. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nature reviews Endocrinology. 2012;8(8):495-502.
14. Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, et al. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. Diabetes care. 2019;42(6):1067-74.

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15. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine. 2015;373(22):2117-28.
16. Chewcharat A, Prasitlumkum N, Thongprayoon C, Bathini T, Medaura J, Vallabhajosyula S, et al. Efficacy and Safety of SGLT-2 Inhibitors for Treatment of Diabetes Mellitus among Kidney Transplant Patients: A Systematic Review and Meta-Analysis. Medical sciences (Basel, Switzerland). 2020;8(4).
17. Mudaliar S, Alloju S, Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. Diabetes care. 2016;39(7):1115-22.
18. Brown E, Wilding JPH, Alam U, Barber TM, Karalliedde J, Cuthbertson DJ. The expanding role of SGLT2 inhibitors beyond glucose-lowering to cardiorenal protection. Annals of medicine. 2021;53(1):2072-89.
19. Green JB, McCullough PA. Roles for SGLT2 Inhibitors in Cardiorenal Disease. Cardiorenal Medicine. 2022;12(3):81-93.