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ORIGINAL PAPER

Sodium-glucose Cotransporter 2 Inhibitors in Kidney Transplant Recipients – A Retrospective Single Center Study

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ABSTRACT

Introduction: Considering the rising occurrence of posttranplant diabetes and the elevated cardiovascular burden among transplant recipients, the utilization of SGLT2 inhibitors (SGLT2i) in this group is appealing because of their cardiovascular and renoprotective benefits. Nevertheless, there is a scarcity of evidence for diabetic kidney transplant recipients (DKTRs) owing to concerns about potential renal graft damage and adverse effects. **Methods:** This retrospective study was devised to assess the effectiveness and safety of SGLT2i in kidney transplant recipients (KTRs). The main focus was on evaluating their impact on parameters such as haemoglobin A1c levels, body mass index (BMI), lipid panel, haemoglobin levels, renal allograft function (estimated glomerular filtration rate) and urirnary protein-to-creatinine ratio. **Results:** A total of 75 renal transplant patients were included in this investigation. The study spanned a median observation period of 18 (2.0–71.0) months. Median estimated glomerular filtration rate at baseline was 61,9 (26–120) mL/min/1.73 m^2 and remained stable throughout the follow-up. Median HbA_{1c} decreased from 7.5 to 7.0% (95% CI; p<0,002). A significant improvement in BMI (95% CI; p<0,001) and lipid panel (95% CI; p<0,05) were also observed. Median haemoglobin rate at baseline was 13,5g/dL and modestly improved at end of follow-up to 13,7g/dL (p=0,12). Regarding urinary protein:creatinine ratio, levels slightly but not significantly rose [+0.05 g/g (p=0,9)]. In a post-hoc subgroup analysis, the rate of urinary tract infections was low (10%). No other side effects were observed during the treatment course. **Conclusions:** This study demonstrates that the administration of SGLT2i is viable and well-tolerated, with no notable side effects observed in KTRs. However, the question of whether SGLT2i can effectively lower cardiovascular mortality and enhance allograft survival in these patients remains to be explored in subsequent studies.

Descriptors: Sodium-Glucose Transport Proteins; Kidney Transplantation; Diabetes Mellitus.

Inibidores do Cotransportador de Sódio-Glicose 2 em Receptores de Transplante Renal – um Estudo Retrospectivo de Centro Único

RESUMO

Introdução: Considerando o aumento da incidência de diabetes pós-transplante e o elevado impacto cardiovascular entre os receptores de transplantes, este facto faz com que o uso de inibidores de SGLT2 nesse grupo seja atrativo devido aos seus benefícios cardiovasculares e renoprotetores. No entanto, há escassez de evidência nos receptores de transplante renal com diabetes devido a preocupações com possíveis danos ao enxerto renal e efeitos adversos. **Métodos:** Este estudo retrospectivo foi elaborado para avaliar a eficácia e segurança dos inibidores de SGLT2 em receptores de transplante renal (KTRs). O foco principal foi avaliar o seu impacto em parâmetros como níveis de hemoglobina A1c, índice de massa corporal (IMC), perfil lipídico, níveis de hemoglobina, função do enxerto renal (taxa de filtração glomerular estimada) e relação proteína/creatinina urinária. **Resultados:** Um total de 75 pacientes receptores de transplante renal foram incluídos em nossa investigação. O estudo abrangeu um período de observação mediano

de 18 (2,0–71,0) meses. A taxa média de filtração glomerular estimada no início foi de 61,9 (26–120) mL/min/1,73 m^2 e permaneceu estável durante o acompanhamento. A mediana da HbA1c diminuiu de 7,5 para 7,0% (IC 95%; p<0,002). A melhora significativa no IMC (IC 95%; p<0,001) e no perfil lipídico (IC 95%; p<0,05) também foram observados. A taxa média de hemoglobina no início foi de 13,5g/dL e melhorou modestamente no final do acompanhamento para 13,7g/dL (p=0,12). Em relação à relação proteína/creatinina urinária, os níveis aumentaram ligeiramente, mas não significativamente [+0,05 g/g (p=0,9)]. Numa análise de subgrupo post-hoc, a taxa de infecções do trato urinário foi baixa (10%). Nenhum outro efeito colateral foi observado durante o curso do tratamento. **Conclusões:** Este estudo demonstra que a administração de inibidores de SGLT2 é viável e bem tolerada, sem efeitos colaterais notáveis em receptores de transplante renal. No entanto, a questão de saber se a inibição do SGLT2 pode efetivamente reduzir a mortalidade cardiovascular e melhorar a sobrevida do enxerto nesses pacientes permanece a ser explorada em estudos subsequentes.

Descritores: Proteínas de Transporte de Sódio-Glucose; Transplante de Rim; Diabetes Mellitus.

INTRODUCTION

In contemporary times, a growing number of diabetic patients undergoing transplantation has been observed, accompanied by a rising incidence of posttransplant diabetes mellitus (PTDM). This trend is attributed to the increased prevalence of obesity and the acceptance of older individuals as potential candidates for transplantation[1].

Following solid organ transplantation, patients may experience elevated blood glucose levels, and up to 40% may develop PTDM. This is significant, considering that mortality during an 8-year follow-up period after kidney transplantation was reported to be 16% among non-diabetic patients but rose to 22% among diabetic patients[2,3].

KTR face an increased risk and expedited development of diabetic micro- and macrovascular complications, influenced by factors like immunosuppression, susceptibility to infections, diminished glomerular filtration rate (GFR), and weight gain after transplantation[1-3]. Furthermore, inadequate glycemic control is a recognized risk factor for infection and delayed graft function, potentially exerting a negative impact on allograft survival. Therefore, ensuring adequate glycemic control is of paramount importance in the care of kidney transplant recipients[4-6].

The management guidelines for PTDM are grounded in the principles established for type 2 diabetes mellitus (T2DM). Insulin frequently becomes a necessary component of PTDM treatment. Additionally, in the realm of oral anti-diabetic medications, dipeptidylpeptidase-4 inhibitors (DPP4i) and SGLT2i have found adoption in clinical practice[2].

SGLT2i represent a relatively recent class of anti-hyperglycemic agents that operate by diminishing glucose reabsorption in the proximal tubule of the kidney, consequently increasing the excretion of glucose in the urine. Beyond their role in reducing hemoglobin A1c (HbA1c) levels by an average of 0.4 to 0.7%, SGLT2i have demonstrated additional benefits in large-scale clinical trials. These include modest weight loss, a decrease in systolic blood pressure, and positive effects on outcomes such as reduced cardiovascular mortality and progression of chronic kidney disease (CKD). In addition to, they have shown efficacy in decreasing proteinuria, hospitalizations due to heart failure, progression of nephropathy, and all-cause mortality in the general population[1,3,5,6].

The significant prevalence of diabetes and cardiovascular disease in renal transplant recipients underscores the potential utility of SGLT2i therapy in this specific population. Nevertheless, it is noteworthy that all major renal outcome trials conducted so far have excluded patients who have undergone renal transplant[5,7].

At present, there is a dearth of large clinical trials providing clear guidance for the management of T2DM and PTDM in solid organ transplant recipients. The guidelines from both the Canadian and American Diabetes Associations suggest selecting anti-hyperglycemic agents based on factors such as the drug's adverse profile (e.g., potential for weight gain) and its interactions with other drugs[2].

Therefore, the results, efficacy and safety of treatment with SGLT2i specifically in DKTRs will be evaluated in hospital centers.

METHODS

A retrospective study was performed involving all adult kidney transplant recipients who commenced treatment with SGLT2i. Eligible patients were those with an eGFR greater than 25 mL/min and no acute kidney injury (AKI) within the 30 days leading up to the initiation of the drug. Two exclusion criteria were defined: individuals with type 1 diabetes (n=2) and individuals submitted to a double kidney and pancreas transplant (n=5).

The primary outcomes of this study encompassed assessments of haemoglobin A1c levels, BMI, lipid panel parameters (including low-density lipoprotein cholesterol, total cholesterol, and triglycerides), hemoglobin levels, renal allograft

function (estimated glomerular filtration rate), and urinary protein-to-creatinine ratio, both at baseline and at the end of the follow-up period.

Secondary outcomes involved the examination of adverse events, such as treated urinary tract infections (UTIs), genital fungal infections, acute kidney injury, euglycemic diabetic ketoacidosis (EDKA), amputations, and episodes of graft rejection.

Patients underwent regular follow-ups during renal transplant consultations, and the introduction of SGLT2i was carried out by team members after providing thorough explanations of the potential side effects.

Statistical analysis

Demographic, clinical, and laboratory data were collected and subjected to analysis using descriptive statistics with SPSS Statistics software. The data were presented as means ± standard error, and comparisons were conducted using the analysis of variance (ANOVA) test. A significance level below 0.05 ($P<0.05$) was considered statistically relevant. The Wilcoxon rank sum test was employed for comparing quantitative data between groups.

Outcome data were meticulously gathered at both baseline and the conclusion of the follow-up period. Potential complications associated with the use of SGLT2i were closely monitored throughout the study duration.

RESULTS

A total of 75 renal transplant patients were included in the study. The mean age of the participants was 60.8 ± 10.6 years, with 68% being men. Among them, 70% presented with post-transplant diabetes. The majority of patients had previously been treated with antidiabetic therapies, primarily insulin (48.1%), followed by DPP4 inhibitors (36.1%), and metformin (33.1%).

Common comorbid conditions included hypertension (89.4%), dyslipidemia (87.5%), and obesity (body mass index > 30) in 15% of the participants. The median duration since transplantation was 11.2 years, with 83% having received a deceased kidney donation and 17% a living donor kidney. Maintenance immunosuppression predominantly involved calcineurin inhibitors (89%) and mycophenolate mofetil (78%), while corticosteroids were administered to 77% of the patients. The study spanned a median observation period of 18 (2.0–71.0) months. Median time between transplantation and start of SGLT2i was 9.1 (0–28) years. Median HbA_{1c} was 7.4% (6.1-12.6%) at baseline. Patients characteristics are shown in Table 1.

Table 1. Baseline characteristics of study patients.

Total, n	75
Age, years	61 (24-81)
Gender, female/male, %	32/68
Living Kidney donation, %	17
Maintenance immunosuppression,%	
Calcineurin inhibitors	89.0
Mycophenolate mofetil	78.0
Corticosteroids	77.0
Median HbA_{1c} , %	11.2
Time since Transplantation, years'	7.4
Posttransplant diabetes mellitus, %	70
Underlying Chronic Disease, %	
Diabetic/hypertensive nephropathy	20
IgA Nephropathy	12
Polycystic Kidney Disease	13.3
Chronic glomerulonephritis	40
Other	50.7
Previous antidiabetic therapies, %	
Insulin	48.1
DPP4 inhibitors	36.1
Metformin	33.1
Comorbid conditions, %	
Hypertension	89.4
Dyslipidemia	87.5
Obesity	15.0

Source: Elaborated by the authors.

Significant reductions in HbA1c and Body Mass Index (BMI), as well as an improved lipid panel were observed

Mean change in HgbA1c was 0.5% [SD 0.89, p=0.002] and mean improvement in BMI was 0.7 kg/m^2 [SD 4.25, p=0.001]. There was also a statistically significant (P value of 0.05) reduction on lipid panel parameters such as low-density lipoprotein (LDL) *cholesterol* [SD 33.5, p=0.015], *total cholesterol* [SD 38.0, p=0.001] *and* triglycerides [SD 110.7, p=0.04]. Median haemoglobin at baseline was 13.5 g/dL and modestly improved at end of follow-up to 13.7 g/dL (p=0.12).

Median estimated Creatinine value at baseline was 1.29 mg/dL and slightly increased throughout the follow-up to 1.33 mg/dL [SD 0.43, p>0.05]. Urine protein to creatinine ratio (uPCR) levels rose slightly but not significantly [+0.06 g/g (SD 0.93, p=0.021) (Table 2 and 3).

The rate of urinary tract infections (UTIs) was low. The incidente of UTIs was similar to historical reports in this high-risk patient population (10%). Two out of eight patients with UTIs had a history of UTI prior to SGLT2i initiation. Infections Were not associated with graft dysfunction or sepsis.

No cases of euglycemic diabetic ketoacidosis (EDKA), acute rejection, amputations or genital infections were observed. No clinically relevant mean changes from baseline in serum potassium or sodium were reported [-0.05 mmol/L; 95% confidence interval].

Table 2. Descriptive statistics of study patients.

		TFG_CKD-EPI	TFG	sCr_initial_mg_dl	sCreat	sUr_initial_mg_dl	sUr_mgdl
Mean		61.938	58.0386	1.3301	1.4187	64.83	68.51
Std. Deviation		22.6836	22.59683	.41789	.43866	27.935	27.597
Percentiles	25	42.040	43.6388	1.1000	1.1000	48.00	48.00
	50	60.610	52.6391	1.2900	1.3300	58.00	61.00
	75	76.370	74.0358	1.5000	1.6700	73.00	83.00

Source: Elaborated by the authors.

Table 3. Descriptive statistics of study patients.

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
HbA1c initial	75	7.553	1.3206	5.5	12.6	6.600	7.200	8.100
Col_T_initial	75	174.61	37.880	106	286	150.00	172.00	192.00
TG_initial	75	171.97	104.447	23	615	107.00	144.00	203.00
HDL_initial	75	50.25	14.109	23	88	39.00	48.00	59.00
LDL_inítial	75	92.413	35.4737	32.0	238.0	74.000	89.000	108.000
Peso_initial	75	74.880	13.5945	47.0	110.0	65.000	72.600	86.000
IMC_initial	75	26.933	5.2681	2.0	41.8	24.440	26.610	30.070
HbA1c_final	75	7.081	.8989	5.3	9.7	6.400	7.000	7.600
Col_T_final	75	161.95	38.015	89	266	128.00	163.00	188.00
TG final	75	161.21	110.756	59	824	106.00	134.00	172.00
HDL_final	73	48.48	13.476	26	98	40.00	46.00	54.00
LDL_final	72	81.58	33.522	21	185	57.50	81.00	100.00
Peso_final	75	73.181	13.9127	47.0	118.0	64.000	75.000	82.000
IMC final	75	26.543	4.5461	18.7	39.0	23.620	26.030	29.030

Source: Elaborated by the authors.

DISCUSSION

SGLT2i have consistently demonstrated notable benefits in terms of renal, cardiovascular, and mortality outcomes across various populations, including individuals with chronic kidney disease, as evidenced by significant trials such as EMPA-KIDNEY Outcome study[8], DAPA-CKD study[9], CANVAS[10], and DECLARE-TIMI58 study[11]. The CREDENCE trial[12], specifically designed to evaluate renal protection, also highlighted the efficacy of canagliflozin.

Furthermore, SGLT2i show potential for improving arterial stiffness, vascular resistance, and cardiac function, as indicated by existing research[5]. The combination of SGLT2i with an ACE inhibitor or ARB has been shown to have an

additive effect, as demonstrated in the CREDENCE study. This effect is attributed to hemodynamic impacts on both the afferent and efferent arterioles[12].

In another study conducted by Yamout et al., a comparison between patients receiving SGLT2i and those receiving a placebo revealed significant decreases in HbA1c, body weight, and systolic blood pressure in the group receiving SGLT2i, as opposed to the placebo group[3].

In terms of glycemic efficacy, the use of SGLT2i, whether employed alone or in conjunction with other glucose-lowering therapies, enhances glycemic control by facilitating glycosuria. SGLT2i results in a reduction of HbA1c levels in individuals with T2DM and preserved renal function, typically by about 0.8%, and does not pose an elevated risk of hypoglycemia compared to placebo. Similar to non-transplant T2DM populations, the most substantial reduction in mean HbA1c levels (approximately -1.93%) was observed in studies where the baseline HbA1c levels were highest (e.g., mean baseline HbA1c level of 9.34%). Overall, the impact of SGLT2i on the reduction of HbA1c levels was found to be comparable between kidney transplant patients with diabetes mellitus (DM) and the non-transplant T2DM population[13].

In this cohort, a statistically significant decrease in the median HbA1c of 0.5% was observed. This aligns with existing data, which also suggests a reduction in HbA1c ranging from 0.2% to 0.6%. The consistent findings across studies reinforce the potential efficacy of the intervention in improving glycemic control among the studied population[13]. Recently, there has been a study specifically investigating empagliflozin after kidney transplantation. In this study, the use of empagliflozin resulted in a significant reduction in HbA1c when compared to the placebo group. It's noteworthy that the extent of glucose reduction was found to be dependent on factors such as eGFR and baseline HbA1c levels. This suggests that the efficacy of empagliflozin in improving glycemic control is influenced by the patient's renal function and the starting level of HbA1c[14].

In this study, a notable reduction in body weight was observed compared to the placebo group. The weight reduction associated with SGLT2i is typically evident within a short period, as early as 3 days after initiating the medication. This rapid effect is likely attributed to the natriuretic and diuretic effects of SGLT2i. Over the long term, the sustained calorie loss through glycosuria induced by SGLT2i has been reported to result in weight loss ranging from 2.0 to 3.5 kg in various studies. However, it's important to note that the degree of weight loss can vary considerably based on individual patient characteristics[15].

Indeed, the impact of SGLT2i on weight reduction is influenced by several factors, including baseline weight, eGFR, and the concurrent use of other medications by the subjects. Individual characteristics and health conditions play a role in determining the extent of weight loss experienced by patients receiving SGLT2i[13].

In this patient cohort, a notable and statistically significant reduction in BMI of 0.7 kg/m2 was observed by the end of the follow-up period. This suggests that the use of SGLT2i contributed to a positive impact on body weight in KTRs[13].

Additionally, it's acknowledged that dyslipidemia is prevalent in kidney transplant patients, often attributed to the adverse effects of immunosuppressive agents. Managing dyslipidemia in this population is crucial, and the observed changes in BMI may have additional implications for cardiovascular risk factors beyond glycemic control[15,16].

Indeed, SGLT2i have been associated with favorable effects on lipid profiles. They may increase high-density lipoprotein cholesterol (HDL-C) levels and decrease plasma low-density lipoprotein cholesterol (LDL-C) and triglyceride levels. These alterations in lipid parameters suggest potential cardiovascular benefits over the long term. The improvements in lipid profiles associated with SGLT2i contribute to their role in addressing cardiovascular risk factors in addition to their primary glucose-lowering effects[15,16].

It's important to note that findings on the effects of SGLT2i on lipid profiles can vary among studies. As reported by Attallah and Yassine, their study indicated an average increase in LDL-C by 5.3 mg/dl and total cholesterol by 4.8 mg/dl within a 12-month period. Importantly, in this study, no significant changes were observed in HDL-C and triglyceride levels[16]. The study conducted by Halden et al. reported a different outcome, noting significantly higher levels of LDL-C, HDL-C, and total cholesterol at the end of the 6-month period[17].

In this cohort, we observed significant reduction on lipid panel such as LDL-cholesterol (average of 10.9 mg/dL), total cholesterol (average of 12.7 mg/dL) and triglycerides (average of 10.7 mg/dL) during the study period[17].

Anemia is a prevalent condition in kidney transplant patients, estimated to affect 30-40% of individuals, and it is recognized as a common risk factor for graft loss and mortality, particularly in the initial three years post-transplant. Recent studies suggest that SGLT2i may play a role in mitigating anemia in KTRs and potentially improving allograft outcomes[18,19].

These studies indicate that SGLT2i can contribute to an increase in hemoglobin levels by approximately 0.6–0.7 g/dL, offering relief from anemia for a significant proportion of patients. Additionally, in patients with heart failure, SGLT2i have demonstrated a 2–3 fold increase in the likelihood of correcting anemia when compared with placebo. These findings

highlight the potential benefits of SGLT2i in addressing anemia, not only in the general population but also in specific patient groups such as KTRs[18,19].

The mechanism behind the observed increase in hemoglobin levels with SGLT2i in kidney transplant recipients is thought to be multifaceted. One proposed explanation is the stimulation of erythropoietin, a hormone that plays a key role in the production of red blood cells. SGLT2i may contribute to an expansion in red blood cell mass, leading to an improvement in hemoglobin levels[19,20].

Additionally, it is suggested that SGLT2i might play a role in neutralizing the functional iron deficiency state commonly seen in patients with anemia of chronic disease, particularly those associated with an inflammatory state. By addressing these underlying factors, SGLT2i could contribute to the correction of anemia in kidney transplant recipients[19,20]. Fructuoso et al. observed significant increases in haemoglobin levels [+0.44 g/dl (95% CI 0.28–0.58][20]. In this study, median haemoglobin rate modestly improved at end of follow-up to 0.2 g/dL (p=0.12) [20].

In this cohort, there wasn't a significant increase in creatinine values (+0.4 mg/dL) concerning renal graft function. This observation aligns with findings from the Derive-Study, where kidney function initially worsened slightly but eventually stabilized[13]. This pattern is consistent with what is commonly observed in patients without a transplant who are receiving SGLT2i. The transient worsening of kidney function is likely attributed to hemodynamic changes induced by SGLT2i[21].

It's essential to recognize that the impact on renal function is often a complex interplay of factors, and understanding the hemodynamic effects of SGLT2i is crucial in interpreting changes in creatinine values in KTRs[13].

The largest numerical reduction in eGFR reported in a study was documented by AlKindi et al., indicating a decrease of -5.87 ml/min/1.73 m2 within 12 months. This reduction in eGFR suggests a potential impact on glomerular hyperfiltration, and thus, it implies a nephroprotective effect associated with SGLT2i in KTRs. This observation is consistent with findings from studies conducted by Schwaiger et al. and Halden et al., which also suggest a decrease in glomerular hyperfiltration in kidney transplant patients, indicating a potential benefit in terms of renal protection[13].

In addition to the positive effects on eGFR, SGLT2i have demonstrated a reduction in urinary protein-to-creatinine ratio (uPCR). In a retrospective study conducted by Attallah and Yassine, where eight renal transplant patients were treated with empagliflozin (25 mg/day), an average decrease in uPCR of 0.6 g/day was observed over a 12-month period. This reduction in uPCR suggests a potential renal protective effect of SGLT2i by decreasing proteinuria, which is often an indicator of kidney damage or dysfunction[16]. In EMPA-REG, urine Protein decreased by 0.6g per day[8].

In this study, patients demonstrated a mild increase in uPCR (+0,06g/g, p=0,9). These results are due to multiple contributors. The fact that their use is only reported in diabetic patients and as an antidiabetic, limits the interpretation of the potential of these drugs as modifiers of the prognosis of CKD in transplant recipients. Besides that, this study has a limitation regarding the large range of follow-up time (2 to 71 months), because it may lead to heterogeneous outcomes, making it difficult to accurately assess and quantify disease progression trends introducing variability in the severity and duration of CKD and uPCR at the time of assessment.

We also present a very high median (11 years) of post-kidney transplantation time, which may predispose to a higher likelihood of chronic graft dysfunction with established glomerulosclerosis and/or transplant glomerulopathy and ensuing higher baseline uPCR. This reduces the potential for proteinuria reduction in these patients. Perhaps this helps to explain the non-reduction of proteinuria observed, which would otherwise be very surprising. This limitation also explains why kidney function worsened slightly in this study along all follow-up time and not only at an initial phase[13].

In summary, current trials involving diabetic patients who have not undergone kidney transplantation have demonstrated that SGLT2i confer cardiovascular and renal protection. Consequently, one might anticipate that the use of SGLT2i in kidney transplant recipients would be beneficial. However, these medications are often withheld in the posttransplant setting due to uncertainties specific to this population. Key concerns include issues related to volume homeostasis, the risk of acute kidney injury (AKI), and the potential for infectious complications[22].

A review by Jenssen et al. assessed the efficacy and safety of SGLT2i in patients with PTDM. The conclusion drawn was that urinary tract infections were not more frequent in KTR than in other patients receiving SGLT2i. Additionally, bacterial genital infections observed in KTR were within the expected range for this population, aligning with findings in patients with T2DM. This suggests that, in terms of infection risks, the use of SGLT2i in kidney transplant recipients may not be substantially different from other patient groups[5].

In this study, urinary tract infections were observed in two patients, reflecting an annual incidence of 0.32 per patient. Notably, the infection course was uncomplicated in all patients and did not lead to the discontinuation of SGLT2i. This incidence rate appears relatively low for kidney transplant recipients (KTRs). Comparatively, Ariza-Heredia et al. reported a similar incidence of 34% during a two-year observation period[22].

It's worth highlighting that in the EMPA-REG trial, the primary significant side effect was found to be genital infections, which were notably more likely in patients receiving empagliflozin[8]. This study did not detect any cases of genital infection during the follow-up period. Additionally, there were no reported cases of euglycemic diabetic ketoacidosis (EDKA), acute rejection, amputations, or urogenital infections among the patients during the treatment course. Furthermore, no clinically relevant mean changes from baseline in serum potassium or sodium were observed.

This profile of safety outcomes in this study aligns with a reassuring risk profile for adverse events associated with SGLT2i initiation post-kidney transplant. The absence of significant adverse events supports the notion that, in this cohort, the use of SGLT2i was generally well-tolerated and consistent with the safety data reported in the existing literature.

This study has acknowledged certain limitations, including its observational nature, which means that neither patients nor physicians were blinded to the treatment, and there was a lack of randomization and a comparator group. Additionally, there were no specific time-course and dose-response studies conducted. These limitations are important to consider when interpreting the findings as they may introduce potential biases and confounding factors.

However, this study also has notable strengths. The extended period of observation and the inclusion of a considerable number of patients enhance the robustness of the data. Furthermore, the study participants represent the broader population of renal transplant recipients with PTDM in clinic, adding a degree of external validity to the findings. Despite the limitations, the study provides valuable insights into the use of SGLT2i in this specific patient population.

In summary, this study globally suggested that the use of SGLT2i among diabetic renal transplant patients is viable and well-tolerated. The findings from this study align with the limited available data to date, further contributing to the understanding of the potential benefits and safety profile of SGLT2i in this specific patient population.

CONCLUSION

In conclusion, the data demonstrate that the use of SGLT2i is not only feasible but also well-tolerated among renal transplant recipients, opening the door to potential novel therapeutic approaches for improving long-term outcomes post kidney transplantation. The findings suggest that SGLT2i could represent a promising treatment option for this specific patient population.

However, recognizing that the full underlying physiology of the renal protective effects of SGLT2i in kidney transplant patients remains uncertain, rightly emphasize the need for further long-term randomized controlled trials in this population. These studies would provide critical insights into the safety and efficacy of SGLT2i, including their impact on mortality reduction, and contribute to a more comprehensive understanding of their role in the management of renal transplant recipients.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Freitas J, Francisco JT, Coimba MT, Carvalho R, Vilela S, Silvano JL, Ribeiro C, Malheiro J, Pedroso S, Almeida M, Fonseca I, Martins LS **Conception and design:** Freitas J, Martins LS **Data analysis and interpretation:** Freitas J , Fonseca I **Article writing:** Freitas J, Silvano JL **Critical revision:** Martins LS **Final approval:** Martins LS

DATA AVAILABILITY STATEMENT

All data were generated or analyzed in this study.

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