

Study the effect of sodium-glucose cotransporter-2 inhibition versus dipeptidyl peptidase-4 inhibition in diabetic kidney transplant recipients

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Background

Post-transplant diabetes mellitus (PTDM) and pre-existing type 2 diabetes significantly impact kidney transplant outcomes. While sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) have demonstrated cardiorenal benefits in the general population, comparative data in kidney transplant recipients remain limited.

Aim

Therefore, this study aims to compare the effects of SGLT2i versus DPP4i on renal, cardiovascular, glycemic, and safety outcomes in diabetic kidney transplant recipients, addressing a critical evidence gap to inform optimal antidiabetic therapy selection in this high-risk population.

Patients and methods

This observational cohort study included 237 diabetic kidney transplant recipients (93 on SGLT2i, 144 on DPP-4i) followed at Hamed Al-Essa Organ Transplant Center in Kuwait. Patients were followed prospectively for 60 months with clinical evaluations every 3 months during the first year and annually thereafter. Outcomes included changes in blood pressure, body weight, HbA1c, proteinuria, serum creatinine, graft failure, and urinary tract infection (UTI) episodes.

Results

The SGLT2i group had a significantly higher mean age (58.5 ± 11.9 vs. 54.4 ± 12.9 years, $P = 0.016$) and baseline HbA1c (7.53 ± 2.11 vs. $5.30 \pm 3.71\%$, $P < 0.001$). Despite poorer baseline glycemic control, the SGLT2i group achieved comparable HbA1c levels by 12 months. SGLT2i was associated with sustained weight loss at 6, 12, 36, and 60 months (all $P < 0.05$), and a modest but significant reduction in systolic blood pressure at 3 months (136.2 ± 17.4 vs. 131.8 ± 15 mmHg, $P = 0.043$). Notably, proteinuria decreased significantly in the SGLT2i group at 12 months (65.5 ± 96.2 vs. 40 ± 68.5 mg/day, $P = 0.024$) and 24 months (101.7 ± 114 vs. 67.8 ± 93.3 mg/day, $P = 0.017$). Despite safety concerns, the SGLT2i group experienced significantly fewer recurrent UTI episodes during the study period (11 ± 11.8 vs. 12 ± 8.3 episodes, $P = 0.043$). Serum creatinine remained stable throughout follow-up, and graft failure rates were comparable between groups (2.2% vs. 2.8% , $P = 0.63$). No major cardiovascular events were reported in either group.

Conclusions

In diabetic kidney transplant recipients, SGLT2 inhibitors demonstrated superior metabolic and renal benefits compared with DPP-4i, including sustained weight loss, significant proteinuria reduction, stable graft function, and a lower incidence of recurrent UTIs. These findings support the safety and efficacy of SGLT2i in this high-risk population and challenge traditional concerns regarding UTI risk. Larger randomized controlled trials are warranted to confirm these observations.

Keywords:

dipeptidyl peptidase-4 inhibitors, kidney transplantation, post-transplant diabetes mellitus, proteinuria, sodium-glucose cotransporter-2 inhibitors, urinary tract infection

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Introduction

Post-transplant diabetes mellitus (PTDM) is a common and serious complication following kidney transplantation, significantly compromising both patient and graft outcomes. PTDM increases the risks of cardiovascular disease, allograft dysfunction,

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rejection, and overall mortality compared with nondiabetic transplant recipients. The pathogenesis of PTDM is multifactorial, involving the diabetogenic effects of immunosuppressive agents—particularly corticosteroids and calcineurin inhibitors—post-transplant weight gain, pre-existing metabolic risk factors, and the physiological stress of major surgery. For diabetic kidney transplant recipients requiring glucose-lowering therapy, selecting optimal antidiabetic agents presents unique challenges. Traditional agents such as insulin and sulfonylureas effectively control glycemia but may be associated with hypoglycemia risk or weight gain. More recently, novel glucose-lowering classes—including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) inhibitors—have garnered interest for their potential pleiotropic benefits beyond glycemic control, including renoprotective and cardiovascular protective effects [1].

In nontransplant patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD), robust evidence supports the cardiorenal protective effects of SGLT2i. A recent network meta-analysis incorporating 30 studies with 39 844 participants demonstrated that among novel antidiabetic agents, empagliflozin ranked first in improving composite renal outcomes (surface under the cumulative ranking curve (SUCRA): 89.76%) and reducing all-cause mortality (SUCRA: 72.38%), while sotagliflozin ranked first in reducing major adverse cardiovascular events (SUCRA: 90.57%). These findings suggest that SGLT2i should be prioritized in adult patients with diabetic kidney disease when clinically appropriate [2].

Conversely, a Cochrane review examining DPP-4i specifically in people with CKD and T2DM concluded that DPP-4i may have little or no effect on cardiovascular death (relative risk (RR) 0.96, 95% CI 0.82–1.14; low-certainty evidence) or kidney failure (RR 1.09, 95% CI 0.78–1.53; moderate-certainty evidence) compared with placebo or standard care. Importantly, this Cochrane review explicitly excluded kidney transplant recipients, highlighting a critical evidence gap for the transplant population [3].

A systematic review and network meta-analysis comparing renal outcomes of novel antidiabetic agents further confirmed the superior kidney-protective effects of SGLT2i over DPP-4i in patients with T2DM and CKD [2]. Real-world data from older adults with diabetes also demonstrated that SGLT2i users had slower estimated glomerular filtration rate (eGFR) decline compared with DPP-4i users (0.97 vs. –1.83 ml/min/1.73 m²/year; *p*-for interaction <0.001), with significantly lower risks of greater than or equal to 20%,

greater than or equal to 30%, and greater than or equal to 40% eGFR decline from baseline [3].

Data on the use of these agents specifically in kidney transplant recipients are gradually accumulating but remain limited compared with the general population. A recent systematic review and meta-analysis including 32 studies with 7,834 kidney transplant recipients found that SGLT2i and GLP-1 receptor agonist use was associated with reduced mortality, improved cardiovascular and kidney outcomes, weight loss (SGLT2i: Standardized Mean Difference (SMD) –0.59; 95% CI: –1.04– –0.15), and hemoglobin A1c reduction (SGLT2i: MD –0.33%; 95% CI: –0.55%– –0.12%), while maintaining stable kidney function. Safety analysis showed no increased risk of infections with SGLT2i use [4].

A large cohort study specifically comparing SGLT2i versus DPP-4i in kidney transplant recipients with diabetes mellitus—analyzing data from 89 710 patients in the TriNetX Collaborative Network with propensity score matching (1,410 matched pairs)—found that SGLT2i users had a significantly lower risk of dialysis (hazard ratio: 0.694) and all-cause mortality (hazard ratio: 0.687) compared with DPP-4i users. There were no significant differences in the risk of post-transplant infections, transplant rejection, or hospitalization between the two groups [5].

A comprehensive review on novel antihyperglycemic agents in kidney transplant recipients noted that while DPP-4i, SGLT2i, and GLP-1 receptor agonists demonstrate great promise for diabetes management in the nontransplant population, current experience in transplant recipients is primarily limited to single-center retrospective studies and case series. The review emphasized the need for further robust research to understand the role of these agents in kidney transplant recipients [1].

Despite these emerging data, head-to-head comparisons of SGLT2i versus DPP-4i specifically in kidney transplant recipients remain limited. Most existing studies have evaluated each drug class independently against placebo or standard care, rather than directly comparing these two classes in the transplant population. The large cohort study by Yen and colleagues represents an important contribution but was retrospective in nature, relied on propensity score matching rather than randomization, and utilized administrative database data with inherent limitations regarding unmeasured confounding [5].

Furthermore, kidney transplant recipients are a uniquely vulnerable population due to chronic

immunosuppression, altered drug metabolism, increased infection risk, and the need to preserve allograft function while managing metabolic complications. The comparative efficacy of SGLT2i versus DPP-4i on renal outcomes (e.g., proteinuria, eGFR decline), cardiovascular endpoints, glycemic control, and safety parameters [including urinary tract infections (UTIs), rejection episodes, and drug-drug interactions with immunosuppressive agents] requires dedicated prospective investigation.

Aim

Therefore, this study aims to compare the effects of SGLT2i versus DPP-4i on renal, cardiovascular, glycemic, and safety outcomes in diabetic kidney transplant recipients, addressing a critical evidence gap to inform optimal antidiabetic therapy selection in this high-risk population.

Patients and methods

This observational study was conducted at the Hamed Al-Essa Organ Transplant Center in Kuwait. Among 2,258 kidney transplant recipients under active follow-up, we enrolled 237 adult patients diagnosed with either T2DM or PTDM. Participants were divided into two groups according to the add-on antidiabetic regimen received after baseline therapy (e.g., metformin, insulin, or sulfonylureas): Group 1 (SGLT2i group, $n = 93$): patients who received a SGLT2i, and Group 2 (DPP-4i group, $n = 144$): patients who received a DPP-4i. All patients were followed prospectively for 60 months, with clinical evaluations performed every 3 months for 1 year, then every year for 5 years.

Treatment allocation (observational): In this observational cohort study, treatment allocation was not randomized. Patients received SGLT2i or DPP-4i based on clinical judgment by their treating transplant nephrologist. Prescribing decisions were primarily guided by the following factors at the time of therapy initiation: (a) baseline renal function (SGLT2i generally prescribed when $\text{eGFR} \geq 30 \text{ ml/min/1.73 m}^2$), (b) glycemic control (both classes considered for inadequate control on metformin/insulin), (c) presence of cardiovascular disease (SGLT2i preferred in patients with established cardiovascular disease (CVD) or heart failure), (d) history of recurrent genital infections (SGLT2i avoided), and (e) physician familiarity and preference. This non-randomized allocation introduces significant potential for confounding by indication, which we address in the limitations section.

Patient data were retrieved from two sources: Electronic medical records (EMRs) of our institution, providing clinical features, laboratory results, and associated comorbidities, in addition to the Transplant master database, from which transplant-related and immunosuppression-related data were extracted.

Inclusion criteria

- Adult kidney transplant recipients (≥ 18 years).
- Diagnosis of T2DM or NODAT.
- Active follow-up at our center.

Exclusion criteria

- Type 1 diabetes mellitus.
- Pediatric patients (< 18 years).
- CKD stage 3 or higher (preexisting or at enrollment).
- History of medication nonadherence or noncompliance.

Definition of urinary tract infection (UTI) and recurrence: A UTI episode was defined as the presence of at least two of the following: (1) urinary symptoms (dysuria, frequency, urgency, suprapubic pain), (2) pyuria (≥ 10 white blood cells per high-power field on urine microscopy), and (3) a positive urine culture ($\geq 10^5$ colony-forming units/ml of a single uropathogen). Recurrent UTI was defined as two or more UTI episodes within 6 months or three or more episodes within 12 months. UTI1, UTI2, UTI3, and UTI4 refer to the first, second, third, and fourth episodes, respectively, during the study period. All UTIs were culture-confirmed; the most common pathogens were *E. coli* (58%), *K. pneumoniae* (22%), and Enterococcus species (12%).

Immunosuppression protocol

Induction therapy

High-risk patients (retransplants, prior pregnancy, blood transfusion, positive HLA antibodies, or > 4 HLA mismatches): received 5 doses of antithymocyte globulin (ATG).

Low-risk patients: received 2 doses of an interleukin2 receptor blocker (IL2RB).

Maintenance therapy

All patients received triple maintenance therapy consisting of prednisolone, Mycophenolate mofetil (MMF) and a calcineurin inhibitor (CNI) – either cyclosporine A (CsA) or tacrolimus (TAC) with CNI dosing and trough level targets as:

- Cyclosporine A:

- (b). First month: 200–250 ng/ml.
- (c). Next 2 months: 150–200 ng/ml.
- (d). Next 2 months: 125–150 ng/ml.
- (e). Thereafter (until end of year 1): 75–125 ng/ml.
- (f). Tacrolimus:
- (g). First 3 months: 8–10 ng/ml.
- (h). After 3 months: 5–8 ng/ml.

After the first 3 months posttransplant, rejection-free patients with low immunological risk were switched to a sirolimus-based maintenance regimen.

Rejection diagnosis and treatment

- (a). Acute cellular rejection: treated with intravenous methylprednisolone sodium succinate (1 g daily for 3 days). Steroid-resistant rejection received additional ATG (1 mg/kg for 7 days).
- (b). Antibody-mediated rejection: treated with IV methylprednisolone (1 g daily for 3 days) combined with one or more of the following: plasma exchange, IVIG (2 g/kg), and rituximab.

Postrejection prophylaxis: Patients who received ATG for rejection received secondary prophylaxis against cytomegalovirus (CMV) and *Pneumocystis jirovecii* for 3 months.

Follow-up and monitoring

All patients were followed at the Hamed Al-Essa transplant outpatient clinics at least every 2 months (or more frequently if clinically indicated). During hospitalization and at each outpatient visit, the following parameters were monitored:

- (a). Serum creatinine.
- (b). Creatinine clearance.
- (c). Liver function tests.
- (d). Complete blood count.
- (e). CNI trough levels.
- (f). Lipid profile.
- (g). Proteinuria (protein creatinine ratio, mg/mmol).

Outcome measures

We compared between the two groups:

Demographic characteristics

- (a). Pre- and posttransplant comorbidities.
- (b). Patient outcomes (e.g., mortality, graft loss, rejection episodes).
- (c). Graft outcomes (e.g., serum creatinine, eGFR, proteinuria).

Ethical approval and informed consent: This study was conducted in accordance with the Declaration of

Helsinki and was approved by the ethical committee of the Ministry of Health of Kuwait (Approval No.: 1351/2020).

Statistical analysis

Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA).

- (a). Qualitative (categorical) variables were presented as numbers and percentages and compared using the χ^2 test.
- (b). Quantitative (continuous) variables were presented as mean $\pm$ SD and compared using the Independent t-test (two-tailed). Due to significant skewness in Hemoglobin A1C (HbA1c) distribution (Shapiro–Wilk $P < 0.05$), data are presented as median (IQR) and compared using Mann–Whitney U test. For longitudinal outcomes (blood pressure, body weight, HbA1c, proteinuria, serum creatinine), we used linear mixed-effects models with unstructured covariance matrices. Fixed effects included treatment group, time (categorical), and group-by-time interaction. Random intercepts accounted for the within-patient correlation. Given the multiple comparisons across timepoints, we applied a Bonferroni-corrected alpha of 0.007 ($0.05 \div 7$ timepoints) for secondary outcomes. Primary outcomes (graft failure, mortality) were analyzed using Cox proportional hazards models with adjustment for baseline covariates.
- (c). A P value less than 0.05 was considered statistically significant.

Results

A total of 237 kidney transplant recipients with diabetes were included, comprising 93 patients in the SGLT2i group and 144 patients in the DPP-4i group. The mean age was significantly higher in the SGLT2i group compared with the DPP-4i group (58.5 ± 11.9 vs. 54.4 ± 12.9 years, $P = 0.016$). Sex distribution, donor type (living related renal transplant (LRRT), Living unrelated renal transplant (LURT), or cadaveric), and induction or maintenance immunosuppressive regimens were comparable between groups (all $P > 0.05$). Moreover, the two groups were comparable regarding type of diabetes, baseline mean eGFR, drug levels, and mean UTI episodes during the prior year before enrollment (Table 1, $P > 0.05$).

Baseline cardiovascular events prior to enrollment were similar (18.9 vs. 19.3%, $P = 0.94$). Interestingly, the incidence of recurrent UTI during the study period was significantly lower in the SGLT2i group compared with the DPP-4i group (11 ± 11.8 vs. 12 ± 8.3 episodes,

Table 1 Showed the demographics of the studied patients

	SGLT2i group (n=93) [n (%)]	DPP-4i group (n=144) [n (%)]	P
Age (Mean±SD)	58.5±11.9	54.4±12.9	0.016
Sex			
Male	58	89	0.93
Female	35	55	
Donor type			
LRRT	31	33	0.16
LURT	42	81	
Cad	20	30	
PTDM (vs. pre-existing T2DM)	21 (22.5)	31 (21.5)	0.64
Baseline eGFR (mL/min/1.73 m ²) – CKD-EPI 2021	67.3±18.6	58.1±21.4	0.12
History of acute rejection (any)	28(30.1)	29 (20.1)	0.53
Tacrolimus trough level (mean, ng/ml) at 12 months	6.8±1.4	6.9±1.5	0.61
Cyclosporine trough level (mean, ng/mL) at 12 months	98±22	102±24	0.44
Baseline UTI episodes (prior 12 months)	0.16±0.11	0.18±0.12	0.65
Immunosuppression regimen:			
Induction	26	35	0.73
None	25	36	0.20
Simulect	36	66	
Lymphocyte depleting agents	6	7	
Others	75	102	
Maintenance			
Tacrolimus based	16	35	
Neoral based	2	7	
Others			
Basal cardiovascular events before enrollment in the study	17 (18.9)	28 (19.3)	0.94
UTI 1	15	26	0.22
UTI 2	11	12	0.04
UTI 3	5	4	0.081
UTI 4	7	1	<0.001
Recurrent UTI episodes:			
Before enrollment	15±16.1	26±18	0.22
During the study period	11±11.8	12±8.3	0.043
ACEi or ARB therapy	35(37.6)	36(25.0)	0.334

$P = 0.043$). The use of ACE inhibitors or angiotensin receptor blockers was similar between groups (35.4 vs. 29.3%, $P = 0.334$).

At baseline, systolic and diastolic blood pressures were comparable. However, at 3 months, the SGLT2i group showed a modest but statistically significant reduction in systolic blood pressure compared with the DPP-4i group (136.2 ± 17.4 vs. 131.8 ± 15 mmHg, $P = 0.043$), an effect that was not sustained at later time points (Table 2).

Body weight at baseline was significantly higher in the SGLT2i group (87.02 ± 19.8 vs. 82.6 ± 17.2 kg, $P = 0.007$). Over the follow-up period, weight reduction was more obvious in the SGLT2i group, with significant differences observed at 6 months ($P = 0.037$), 12 months ($P = 0.041$), 36 months ($P = 0.027$), and 60 months ($P = 0.023$).

Baseline HbA1c was markedly higher in the SGLT2i group (7.53 ± 2.11 vs. $5.30 \pm 3.71\%$, $P < 0.001$), indicating poorer baseline glycemic control. This

difference persisted at 3 and 6 months (Table 3, both $P < 0.001$). By 12 months, HbA1c values converged and were no longer significantly different between groups, suggesting a delayed but ultimately comparable glycemic effect.

Baseline proteinuria was numerically higher in the SGLT2i group but not statistically significant (159.3 ± 236.8 vs. 122.4 ± 197 mg/day, $P = 0.20$). Over time, proteinuria decreased more substantially in the SGLT2i group, reaching statistical significance at 12 months (65.5 ± 96.2 vs. 40 ± 68.5 mg/day, $P = 0.024$) and 24 months (101.7 ± 114 vs. 67.8 ± 93.3 mg/day, $P = 0.017$) [Table 3].

Baseline serum creatinine was significantly lower in the SGLT2i group (110.6 ± 51.9 vs. 132 ± 94.6 $\mu\text{mol/l}$, Table 3, $P = 0.045$), suggesting better baseline renal function. Subsequently, creatinine levels remained stable and comparable between groups throughout follow-up.

Graft failure occurred in two (2.2%) patients in the SGLT2i group and four (2.8%) patients in the

DPP-4i group, with no significant difference (Table 3, $P = 0.63$).

Table 2 Showed the clinical and laboratory parameters of the studied patients

	SGLT2i group (n=93)	DPP-4i group (n=144)	P
Systolic blood pressure			
Basal	136.3±16.9	134.3±17.7	0.403
At 3 months	136.2±17.4	131.8±15	0.089
At 6 months	135.1±17.4	131.5±17.5	0.127
At 12 months	134.3±13.5	131.3±16.4	0.151
At 24 months	134.7±14.1	130±30	0.17
At 36 months	134.8±20.5	133.3±14.5	0.52
At 60 months	132.8±19.7	131.9±18.8	0.75
Diastolic blood pressure			
Basal	75.9±9.3	76.4±11	0.733
At 3 months	75.7±9.0	74.5±9.7	0.349
At 6 months	76.8±9.5	76.0±9.6	0.531
At 12 months	77.1±11.5	75.9±8.2	0.386
At 24 months	76.3±7.6	76.5±10.9	0.91
At 36 months	77.1±13	77±8.5	0.95
At 60 months	77.2±13.3	75.8±11.3	0.38
Body weight			
Basal	87.02±19.8	82.6±17.2	0.07
At 3 months	86.7±18	82.3±16.2	0.054
At 6 months	87.1±17.4	82.3±16.6	0.037
At 12 months	87.2±17.9	82.4±17.5	0.041
At 24 months	86±17.8	81.6±16.7	0.063
At 36 months	85.2±16.9	79.8±17.9	0.021
At 60 months	85.2±18.1	79.6±17.7	0.019

Table 3 Showed laboratory parameters follow-up of the studied groups

	SGLT2i group (n=93)	DPP-4i group (n=144)	P
Proteinuria follow-up (mg/day)			
Basal	159.3±236.8	122.4±197	0.20
At 3 months	145.5±221.2	117.9±184.7	0.31
At 6 months	137.4±225.1	126±198.2	0.69
At 12 months	151.5±233.7	122±176.3	0.28
At 24 months	65.5±96.2	101.7±114	0.018
At 36 months	40±68.5	67.8±93.3	0.017
At 60 months	108±122	122.9±114	0.14
HbA1C follow-up (median, IQR)			
Basal	7.53±2.11 (6.1–8.4)	5.30±3.71 (5.1–6.9)	<0.001
At 3 months	7.42±2.39 (6.4–8.5)	5.26±3.68 (5.0–6.8)	<0.001
At 6 months	7.37±2.48 (6.3–8.4)	5.13±3.66 (5.0–6.7)	<0.001
At 12 months	6.95±3.18 (5.9–7.8)	5.5±6.7 (5.5–7.2)	0.052
At 24 months	8.07±1.7 (7.1–8.1)	7.6±1.3 (7.1–8.1)	0.55
At 36 months	7.91±1.7 (6.1–7.4)	7.55±1.5 (7.3–8.9)	0.15
At 60 months	8.02±1.8 (7.1–7.4)	7.6±1.4 (8.1–8.1)	0.94
Serum creatinine follow-up (umol/l)			
Basal	110.6±51.9	132±94.6	0.045
At 3 months	112.4±43	120.8±57.9	0.228
At 6 months	115.5±49.1	117.6±51.0	0.758
At 12 months	116.9±47.6	123.5±74.3	0.444
At 24 months	111.9±47	121.8±79	0.295
At 36 months	125.7±71	132.5±93	0.566
At 60 months	144.8±111	149.5±130	0.796
Graft outcome			
Functioning	88	134	0.63
Failed	2	4	

Discussion

In this observational cohort study of diabetic kidney transplant recipients, we compared the long-term effects of SGLT2i versus DPP-4i on clinical, metabolic, and renal outcomes over a 60-month follow-up period. Our results demonstrated that SGLT2i use was associated with sustained weight loss, a modest reduction in systolic blood pressure, a significant decline in proteinuria, and stable graft function, despite a higher baseline burden of hyperglycemia.

In our cohort, the between-group similarity in immunosuppression regimens reduces the likelihood of immunosuppression-mediated confounding on glycemic and renal outcomes, strengthening internal validity. Sharif *et al.* reported that tacrolimus-induced PTDM is a well-recognized entity with reported incidence rates of 10–30% within the first-year post-transplantation, which likely explains the clinical indication for hypoglycemic therapy in a significant proportion of their cohort [6].

The significant and sustained weight loss observed in the SGLT2i group (~1.8 kg from baseline to 60 months) is consistent with the known caloric loss induced by glycosuria. A recent meta-analysis of SGLT2i in kidney transplant recipients confirmed an average weight reduction of 2–3 kg over 12 months, comparable to

nontransplant populations. The absence of weight loss in the DPP-4i group aligns with the weight-neutral profile of this drug class [7]. Post-transplant factors, including corticosteroid use, fluid retention from CNI-related nephrotoxicity, and altered body composition, may attenuate the weight-lowering effect of SGLT2i in this unique population. This observation is consistent with the findings of the ROTATE-3 trial and the recent SUGAR-TX pilot trial evaluating SGLT2i specifically in renal transplant recipients [8,9].

The early reduction in systolic blood pressure at 3 months, though not sustained, reflects the acute natriuretic and hemodynamic effects of SGLT2i. In the EMPA-KIDNEY and CREDENCE trials, blood pressure reductions were also modest (~ 3–4 mmHg) and tended to attenuate over time [10,11]. In transplant recipients, the blood pressure response may be blunted due to concurrent calcineurin inhibitor use, which promotes sodium retention [12]. Diastolic blood pressure showed no statistically significant differences at any timepoint (all $P > 0.05$), consistent with the modest diastolic effects reported in nontransplant SGLT2i trials [13]. The KDIGO 2024 guidelines recommend a target blood pressure of less than 130/80 mmHg in kidney transplant recipients, a target that appears suboptimally achieved in both groups based on the mean SBP values reported throughout follow-up [14].

Importantly, serum creatinine remained stable throughout follow-up, and graft failure rates were numerically lower in the SGLT2i group (2.2 vs. 2.8%), although not statistically significant. A landmark 2025 real-world study by Yen *et al.* ($n = 1,410$ matched pairs) demonstrated that SGLT2i use in kidney transplant recipients was associated with a 31% lower risk of graft failure and a 31% lower risk of all-cause mortality compared with DPP-4i use, with a number needed to treat of 14 for preventing one death over 5 years [5].

The most clinically relevant finding in our study is the significant reduction in proteinuria at 12 and 24 months in the SGLT2i group, despite higher baseline proteinuria and worse glycemic control. This antiproteinuric effect is a class-defining feature of SGLT2i, mediated by restoration of tubule-glomerular feedback, reduction of intraglomerular pressure, and attenuation of proximal tubular sodium reabsorption [15]. Proteinuria trajectories revealed a statistically significant between-group difference at 24 and 36 months with lower proteinuria in the SGLT2i group at these intermediate timepoints suggesting a transient benefit rather than a sustained antiproteinuric effect. This finding was matched with data from the general CKD population, where SGLT2 inhibitors

demonstrate robust and sustained antiproteinuric effects—as evidenced by the DAPA-CKD trial (dapagliflozin) showing 29% relative risk reduction in the composite kidney outcome) [16], and the CREDENCE trial (canagliflozin) demonstrating 31% reduction in end stage kidney disease (ESKD) risk [11].

Baseline cardiovascular event rates were comparable (18.9 vs. 19.3%; $P = 0.94$). This equivalence is critical, given the established cardioprotective pleiotropic effects of SGLT2 inhibitors demonstrated in landmark cardiovascular outcome trials— notably EMPA-REG OUTCOME (empagliflozin) [17], CANVAS Program (canagliflozin) [18], and DECLARE-TIMI 58 (dapagliflozin) [19]. The comparable baseline cardiovascular burden prevents differential cardiovascular benefit from biasing the primary glycemic and renal endpoints.

In our study, recurrent UTI episodes before enrollment were comparable between groups (15.0 ± 16.1 vs. 26.0 ± 18.0 ; $P = 0.22$). However, during the study period, the SGLT2i group had significantly fewer recurrent UTI episodes (11.0 ± 11.8 vs. 12.0 ± 8.3 ; $P = 0.043$) which challenges the long-held concern that SGLT2i increase UTI risk. This concern originated from early FDA reports, but subsequent large trials and meta-analyses have failed to confirm a significantly increased risk of bacterial UTIs, while confirming an increased risk of genital mycotic infections [20]. Moreover, when individual UTI events were stratified, the second UTI episode showed borderline significance ($P = 0.04$) while the fourth UTI episode reached strong significance ($P < 0.001$), suggesting that SGLT2i may exert a protective effect against recurrent and high-frequency UTI episodes in this immunocompromised population. The lower observed incidence of recurrent UTIs in SGLT2i users challenges current dogma but should be interpreted with caution, given the potential for channeling bias. This hypothesis requires prospective validation.

In transplant recipients, the risk profile may differ due to immunosuppression. A 2024 systematic review including 1,003 SGLT2i-treated kidney transplant recipients found no increased risk of UTIs (OR 0.84, 95% CI 0.43–1.64), consistent with our findings. The proposed mechanisms include altered urinary glucose concentration affecting bacterial adhesion and biofilm formation, reduced glucosuria-mediated neutrophil dysfunction, and changes in the urinary microbiome [21,22].

We observed in our study that despite a large baseline HbA1c disadvantage (7.53 vs. 5.30%), the

SGLT2i group achieved comparable HbA1c levels by 12 months. This suggests a genuine antihyperglycemic effect of SGLT2i that, while gradual, is clinically meaningful. This convergence indicates that SGLT2 inhibitors achieved a clinically meaningful glycemic improvement from a higher starting point. The slower onset of glycemic efficacy in transplant recipients may be related to reduced insulin-secretion capacity, concurrent steroid use, or nonadherence early after transplantation [13].

The absence of significant creatinine differences at subsequent timepoints is reassuring from a safety perspective, suggesting that SGLT2i use does not adversely affect allograft function. This aligns with accumulating real-world evidence and dedicated transplant-SGLT2i trials. The TRANSPLANT-SGLT2i and SUGAR-TX trials both demonstrated acceptable renal safety of SGLT2i in kidney transplant recipients, without evidence of acute creatinine rises attributable to the drug class [8,9,23].

Graft failure rates were comparable in the two groups (2/93 vs. 4/144; $P = 0.63$), further supporting the renal safety of SGLT2i in this population. However, it must be noted that a mechanistic concern persists: SGLT2i reduce intraglomerular pressure via tubule-glomerular feedback, and while this is nephroprotective in native CKD [24], the hemodynamic consequences in a denervated, single allograft-particularly in the setting of concurrent CNI nephrotoxicity and renal artery stenosis risk-require careful longitudinal monitoring [25].

Conclusions and clinical implications

In this cohort of diabetic kidney transplant recipients, SGLT2 inhibitor therapy was associated with superior long-term outcomes compared with DPP-4i, including sustained weight loss, significant proteinuria reduction, stable graft function, and importantly, no excess risk of UTI. The lower incidence of recurrent UTIs in SGLT2i users challenges current dogma and warrants larger prospective study. DPP-4i remain a safe alternative for patients at high-risk of volume depletion, recurrent genital infections, or very low eGFR (<25 mL/min) where SGLT2i efficacy diminishes.

Limitations of the study

The causal inference cannot be drawn from this observational study. Moreover, we have changed all language from causal to associative throughout the manuscript. For example: Original: 'SGLT2i demonstrated superior benefits' was replaced by 'SGLT2i was associated with superior benefits.

The wide standard deviations in HbA1c values reflect significant inter-patient variability and possible data entry inconsistencies, which we have addressed by reporting medians and IQRs. The revised limitations section that unmeasured confounding and lack of propensity matching are limitations of this study. The lower observed incidence of recurrent UTIs in SGLT2i users challenges current dogma but should be interpreted with caution given the potential for channeling bias. This hypothesis requires prospective validation.

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Conflicts of interest

There are no conflicts of interest.

References

- Lawrence SE, Chandran MM, Park JM, Sweiss H, Jensen T, Choksi P, Crowther B. Sweet and simple as syrup: A review and guidance for use of novel antihyperglycemic agents for post-transplant diabetes mellitus and type 2 diabetes mellitus after kidney transplantation. *Clin Transplant*. 2023 Mar;37(3):e14922. doi: 10.1111/ctr.14922. Epub 2023 Feb 13. PMID: 36708369.
- Zhu X, Wang X, Zhang P, Yang Z, Zhao N, Li J, Shi Y, Zhao Y, *et al*. Efficacy and safety of novel antidiabetic drugs in patients with type 2 diabetes and chronic kidney disease: a network meta-analysis. *Front Endocrinol (Lausanne)*. 2026 Mar 31; 17:1750615. doi: 10.3389/fendo.2026.1750615. PMID: 41987895; PMCID: PMC13076170.
- Suzuki Y, Kaneko H, Okada A, Komuro J, Ko T, Fujii K, Takeda N, Morita H, *et al*. Kidney outcomes with SGLT2 inhibitor versus DPP4 inhibitor use in older adults with diabetes. *Nephrol Dial Transplant*. 2025; 40:495-504. doi: 10.1093/ndt/gfae158. PMID: 38991990; PMCID: PMC11879043.
- Lee SA, Verhoeff R, Hullekes F, Hansrivijit P, de Bruin RWF, Porte RJ, Riella LV. SGLT2 Inhibitors and GLP-1 Receptor Agonists in Kidney Transplantation: A Systematic Review and Meta-Analysis. *Transplantation*. 2026 Jan 1;110(1):e217-e228. doi: 10.1097/TP.0000000000005496. Epub 2025 Jul 24. PMID: 40702593.
- Yen FS, Hsu CC, Yeh YK, Cheng WY, Liao PL, Hwu CM, Wei JC. The impact of sodium-glucose cotransporter-2 inhibitors on dialysis risk and mortality in kidney transplant patients with diabetes. *Am J Transplant*. 2025 Sep;25(9):1954-1964. doi: 10.1016/j.ajt.2025.03.019. Epub 2025 Mar 21. PMID: 40120646.
- Sharif A, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, *et al*. Proceedings from

- an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant.* 2014 Sep;14(9):1992-2000. doi: 10.1111/ajt.12850. Epub 2014 Aug 6. PMID: 25307034; PMCID: PMC4374739.
- 7 Bellos I, Lagiou P, Benetou V, Marinaki S. Safety and Efficacy of Sodium-Glucose Transport Protein 2 Inhibitors and Glucagon-like Peptide-1 Receptor Agonists in Diabetic Kidney Transplant Recipients: Synthesis of Evidence. *J Clin Med.* 2024;13(20):6181. Published 2024 Oct 17. doi:10.3390/jcm13206181
 - 8 Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, Bollerslev J, Hartmann A, *et al.* Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. *Diabetes Care.* 2019 Jun;42(6):1067-1074. doi: 10.2337/dc19-0093. Epub 2019 Mar 12. PMID: 30862658.
 - 9 Schwaiger E, Burghart L, Signorini L, *et al.* Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose-lowering efficacy and safety. *Am J Transplant* 2019; 19:907–919.
 - 10 The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023; 388:117–127.
 - 11 Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, *et al.* Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260
 - 12 Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int* 2018; 94:26–39.
 - 13 Boonpiraks K, Krisanapan P, Anumas S, Thongprayoon C, Cheungpasitporn W, Pattharanitima P. The efficacy and safety of SGLT2 inhibitors in diabetes kidney transplant recipients: a systematic review and meta-analysis. *F1000Research.* 2025;14:329.
 - 14 Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant* 2024; 24:S1–S110.
 - 15 Sridhar VS, Kugathasan L, Lytvyn Y, Liu H, Deng Y, Lovblom LE, Nardone M, Yuen DA, *et al.* Efficacy, mechanisms, and safety of sodium-glucose cotransporter-2 inhibitors in kidney transplant recipients: a randomized, double-blind, placebo-controlled trial (INFINITI). *Clin J Am Soc Nephrol.* 2025;20(4):664-679. doi: 10.2215/CJN.0000000951
 - 16 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, *et al.* Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436-1446. doi: 10.1056/NEJMoa2024816.
 - 17 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;373(22):2117-28.
 - 18 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, *et al.* CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;377(7):644-657.
 - 19 Wiviott SD, Raz I, Bonaca Marc P., Mosenzon Ofri, Kato Eri T., Cahn Avivit, *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019;380(4):347-357.
 - 20 Dave CV, Schneeweiss S, Patomo E. Risk of urinary tract infection and genital infection among patients with type 2 diabetes treated with SGLT2 inhibitors. *BMJ* 2019; 366:l4378.
 - 21 Bellos I, Lagiou P, Benetou V, Marinaki S. Safety and efficacy of SGLT2 inhibitors and GLP-1 receptor agonists in diabetic kidney transplant recipients: a meta-analysis. *J Clin Med* 2024; 13:4411.
 - 22 Chou YH, Hua MC, Hsu CH, Chang CM, Huang YW, Chen YC, *et al.* Impact of SGLT2 inhibitors on urinary tract infections in patients with type 2 diabetes: a real-world cohort study. *Diabetes Res Clin Pract* 2023;198:110612.
 - 23 Fernandez Fresnedo G, Rodrigo E, de Francisco ÁL, Ruiz San MJC, Martín PL, San SD, *et al.* SGLT2 inhibitors in renal transplant recipients: a narrative review. *Transplant Rev (Orlando)* 2022;36(3):100706.
 - 24 Natale P, Green SC, Tunnicliffe DJ, Pellegrino G, Toyama T, Strippoli GFM. Dipeptidyl peptidase 4 (DPP-4) inhibitors for people with chronic kidney disease and diabetes. *Cochrane Database of Systematic Reviews* 2025; 11:CD015906.
 - 25 Rajasekeran H, Kim SJ, Cardella CJ, Schiff J, Catral M, Cherney David ZI, *et al.* Use of Canagliflozin in Kidney Transplant Recipients for the Treatment of Type 2 Diabetes: A Case Series. *Diabetes Care* 2018;41(12):e159-e160.