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REVIEW ARTICLE

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Sodium-glucose cotransporter 2 inhibitors for diabetes mellitus control after kidney transplantation: Review of the current evidence

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Abstract

Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) are promising drugs to treat chronic kidney disease patients with or without diabetes mellitus (DM). Besides improving glycemic control, SGLT2i are cardioprotective and kidney protective and decrease bodyweight, serum uric acid, blood pressure, albuminuria and glomerular hyperfiltration. These effects may benefit graft function and survival in kidney transplant (KT) patients. In this review, we evaluate data on the efficacy and safety of SGLT2i for KT patients with DM. Eleven studies with 214 diabetic KT patients treated with SGLT2i have been reported. SGLT2i lowered haemoglobin A1c and bodyweight. While glomerular filtration rate may be reduced in the short-term, it remained similar to baseline after 3–12 months. In two studies, blood pressure decreased and remained unchanged in the others. There were no significant changes in urine protein to creatinine ratio. Regarding safety, 23 patients had urinary tract infections, 2 patients had a genital yeast infection, one had acute kidney injury, and one had mild hypoglycaemia. No cases of ketoacidosis or acute rejection were reported. In conclusion, the limited experience so far suggests that SGLT2i are safe in KT patients with DM, decrease bodyweight and improve glycemic control. However, some of the benefits observed in larger studies in the non-KT population have yet to be demonstrated in KT recipients, including preservation of kidney function, reduction in blood pressure and decreased proteinuria.

KEYWORDS
chronic kidney disease, diabetic kidney disease, kidney transplant, post-transplant diabetes mellitus, SGLT2 inhibitors, transplantation

SUMMARY AT A GLANCE
A review of the literature on the use of sodium-glucose cotransporter 2 inhibitors for kidney transplant recipients, highlighting the relatively robust data on benefits. What remains to be addressed is the safety of the drug, such as concerns about urinary tract infection.

1 | INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease worldwide and has detrimental consequences for cardiovascular health and mortality.[1–3] Kidney transplantation (KT) is the treatment of choice for end-stage kidney disease, regardless of cause. Diabetes mellitus (DM) is also frequently an unwanted consequence of solid organ transplantation (SOT), due to a variety of nonmodifiable and modifiable risk factors. Nonmodifiable factors include older age, male gender, history of diabetes, genetic polymorphisms, innate immunity, human leucocyte antigen mismatch and deceased donor. Modifiable risk factors include obesity, hypomagnesaemia, hyperuricaemia, hepatitis C and cytomegalovirus infections, vitamin D deficiency, pulse steroid therapy, use of calcineurin inhibitors (especially tacrolimus) and mammalian target of rapamycin inhibitors.[4] Post-transplant diabetes mellitus (PTDM) is defined as the development of persisting hyperglycaemia in KT patient without a history of DM. The incidence is 10%–20% of KT patients within the first year post-transplantation.[5]

Various oral glucose-lowering medications and insulins are available for patients with DM, but KT patients with DM often underuse this wide spectrum due to possible drug interactions with immunosuppressive therapies and the side effect profiles of glucose-lowering medications. Sodium-glucose cotransporter type 2 (SGLT2) inhibitors (SGLT2i) are the most recent family of glucose-lowering agents. They additionally have beneficial effects on blood pressure and bodyweight, and offer kidney and cardiovascular protection. This potentially makes them ideally suited to treat KT recipients.[6,7] In this review, we first provide an overview of SGLT2i for non-KT indications and then discuss potential beneficial effects and the safety profile of SGLT2i in KT patients with DM, by examining data from the current literature.[8–18]

2 | SGLT2 AND SGLT2 INHIBITION

SGLT2 in kidney proximal tubular cells reabsorbs almost 90% of glucose from the glomerular filtrate.[19] SGLT2i induce glycosuria by blocking glucose reabsorption and thus, decrease hyperglycaemia in an insulin-independent manner. SGLT2i are usually well tolerated even though some patients experience genital and urinary infections, due to glycosuria. Besides better glycemic control, SGLT2i reduce bodyweight by inducing daily losses of 60–80 g glucose, which corresponds to 240–320 kcal in patients with normal kidney function.[12] Furthermore, SGLT2i decrease blood pressure, serum uric acid (SUA) levels, albuminuria and glomerular hyperfiltration. When tested for cardiovascular safety in patients with type 2 DM (T2DM), they were found to reduce major adverse cardiovascular events and hospitalization for heart failure and to preserve long-term kidney function in type 2 diabetic patients at high cardiovascular risk.[7] These benefits were confirmed in patients with T2DM and chronic kidney disease (CKD) or heart failure,[6,7] and, more recently, in persons with CKD or heart failure regardless of the presence of DM or abnormal estimated glomerular filtration rate (eGFR) at baseline.[20–22]

Apart from above mentioned effects (glucose lowering, blood pressure reduction, weight reduction), recent findings also indicate that there are other beneficial effects of SGLT2i. The study of Castoldi et al. which examined the effects of empagliflozin on the progression of cyclosporine-A (CsA) nephropathy, in the absence of DM, showed that empagliflozin can reduce the CsA-induced glomerular and tubulo-interstitial fibrosis and renal inflammation.[23] Thus the role of SGLT2i may be even more important given the fact that cyclosporine toxicity is of concern in renal transplant patients.

SGLT2 inhibition also reduce tubular workload and hypoxia. By decreasing glucose and sodium reabsorption, SGLT2i decrease tubular workload and oxygen consumption and alleviate hypoxia. Indeed kidney protective effects of SGLT2 inhibition may be in part explained by increasing haemoglobin and improving mitochondrial function.[24,25]

KT patients usually have significant comorbidities that decrease patient and graft survival.[26] In KT patients, T1DM, T2DM and PTDM are major risk factors for the development of cardiovascular disease, shorter graft survival, and premature death,[5] so better management of KT patients' comorbidities may increase graft and patient survival (Figure 1). Thus, based on their cardioprotective and nephroprotective effects, SGLT2i have appeared to be a promising medication in KT patients with T2DM or PTDM. However, potential benefits should be balanced against possible interactions between SGLT2i and immunosuppressive drugs and the adverse effect profile of SGLT2i, including urinary tract or genital mycotic infections, hypovolemia, and diabetic ketoacidosis (Figure 2).

3 | EXPERIENCE WITH SGLT2 INHIBITION IN KT

Published experience with SGLT2i in KT patients consists of 9 manuscripts and 2 abstracts including 214 patients[8–18] (Table 1). Study

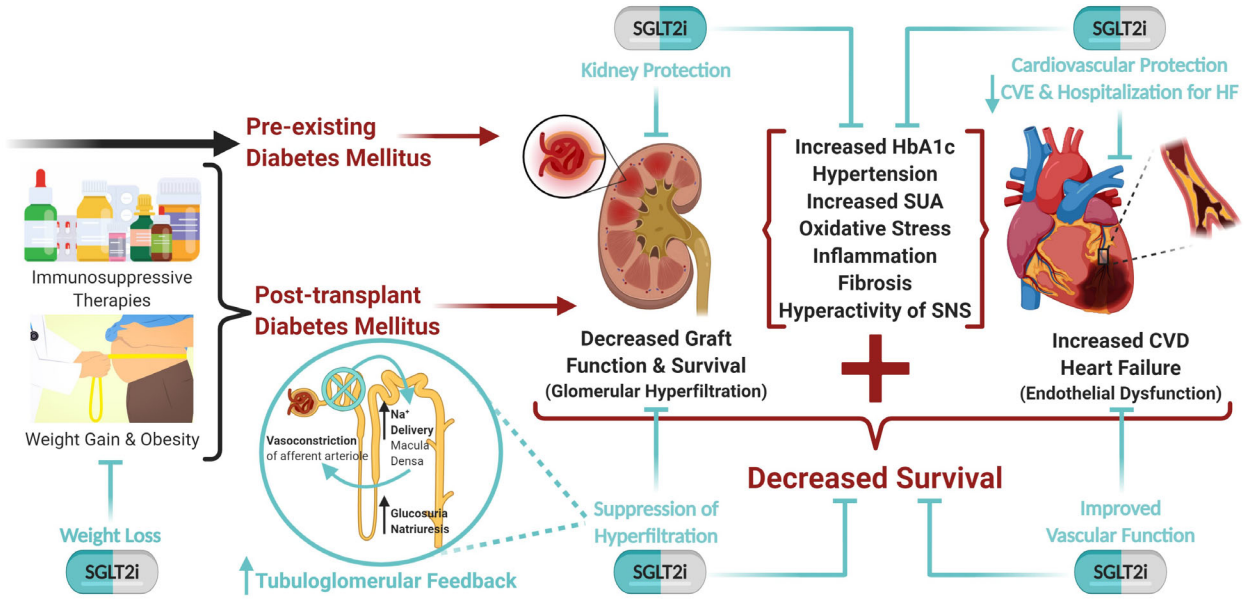

FIGURE 1 Overview for pathogenesis and consequences of diabetes mellitus in kidney transplant patients and effects of sodium-glucose cotransporter type 2 inhibitors (SGLT2i)

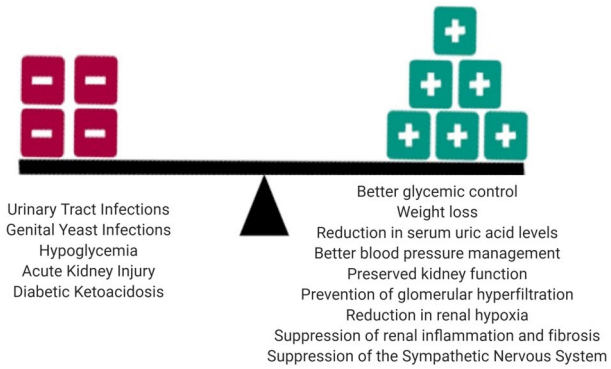

FIGURE 2 Overview of potential postulated unfavourable and favourable effects of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) in kidney transplant patients with diabetes mellitus. CVD, cardiovascular disease; CVE, cardiovascular event; HF, heart failure; Na, sodium; SGLT2i, Sodium, glucose co, transporter, 2 inhibitor; SNS, sympathetic nervous system; SUA, serum uric acid

protocols and population characteristics were markedly different, making comparisons between studies difficult. Ten studies reported the mean duration between study and renal transplantation (Table 1) and the shortest of them was 319.5 days in the study of Song et al.[18] These studies provided data to assess/compare changes in levels of HbA1c, eGFR, blood pressure, and weight after SGLT2i initiation (Table 2). A recent review of Anderson et al. included available data on the usage of dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist besides SGLT2i in the management of KT patients.[27] We specifically focused on the experience of SGLT2i in KT patients with discussing proposed mechanisms for nephroprotective effects of SGLT2i.

4 | EFFECT OF SGLT2i ON GLYCEMIC CONTROL IN KT PATIENTS

Use of SGLT2i either alone or on top of other glucose-lowering therapies improves glycemic control by promoting glycosuria. SGLT2i decrease HbA1c levels in T2DM patients with preserved renal function by about 0.8%[19] and are not associated with an increased risk of hypoglycaemia, compared to placebo. Similar to non-transplant T2DM populations, the 11 studies with 214 KT patients treated with SGLT2i showed a significant decline in HbA1c (Table 2) of ~0.6%. The glucose-lowering effect of SGLT2i decreases with progressively decreasing kidney function.[28] Among the 11 studies, the largest reduction in mean HbA1c level (−1.93%) was observed in the study with the highest mean baseline HbA1c level (9.34%).[10] Kong et al. reported a reduction in mean HbA1c level (−0.5%) after 3 months of treatment, while Halden et al.,[12] Shah et al.,[14] and Kong et al.[17] reported reductions in mean HbA1c level of −0.2%; −0.9%; and −0.4%, respectively within 6 months.[12,14,17] The largest reductions in mean HbA1c levels were observed at the end of 12 months in all studies. Differences in dose, baseline HbA1c and eGFR levels, study design and size could explain the observed differences between various SGLT2i. Only Schwaiger et al. reported an increase in mean HbA1c level (+0.4%) at the end of 12 months. This was likely explained by the study design, as insulin was replaced with a SGLT2i in all patients, while three patients also discontinued other oral glucose-lowering drugs (linagliptin, sitagliptin + metformin, linagliptin) that were used in addition to insulin. Overall, the effects of SGLT2i on the reduction of HbA1c levels was similar between KT patients with DM and the non-transplant T2DM population.

TABLE 1 Studies of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) in kidney transplantation (KT) included in this review

Authors	Country	Study type	*N*	SGLT2i dose/day (*n*)	Follow up (months)	Mean age (years)	Sex (male/female)	% DM prior to KT	Mean duration of renal transplant (years)	Donor (living/dead)
Kwon and Kong[15]	South Korea	NR (Abstract)	25	Dapagliflozin, 5 mg	12	NR	NR	72%	6	NR
Rajasekeran et al.[9]	Canada	Case series	10 [KTR ($n = 6$) SPKTR ($n = 4$)]	Canagliflozin, NR	8	KTR: 61.6 ± 12.6 SPKTR: 49.4 ± 8.9	KTR: 5/1 SPKTR: 2/2	KTR: 83% SPKTR: 75%	KTR: 4.4 ± 3.3 SPKTR: 3.5 ± 3.9	NR
Beshyah et al.[16]	UAE	Case Report	1	Dapagliflozin, 10 mg	30	58	1/0	100%	7	1/0
Schwaiger et al.[8]	Austria	Prospective, interventional, noninferiority pilot	14	Empagliflozin, 10 mg	12 ($n = 8$)	56.5 ± 7.9	7/7	0%	5.8 ± 4.8	NR
AlKindi et al.[10]	UAE	Retrospective chart review	8	Empagliflozin, 10 mg (5), 25 mg (1); dapagliflozin, 5 mg (2)	12	56.8 ± 13.7	6/2	25%	9.6 ± 6.4	8/0
Attallah and Yassine[11]	UAE	Case report	8	Empagliflozin, 25 mg	12	45.9 ± 6.6	4/4	50%	1.7 ± 0.5	7/15
Halden et al.[12]	Norway	Single center, double-blind RCT	22	Empagliflozin, 10 mg	6	63 (31, 72)	17/5	0%	3	9/13
			22 (control)	Placebo	6	59 (21, 75)	17/5	0%	3	7/15
Mahling et al.[13]	Germany	Prospective observational	10	Empagliflozin, NR	12	66 (56, 73)	8/2	60%	5.9 (4.4, 8.8)	8/2
Shah et al.[14]	India	Prospective observational	24	Canagliflozin, 100 mg	6	53.8 ± 7.1	23/1	83%	2.7 (0.2, 13.2)	NR
Kong et al.[17]	South Korea	NR (Abstract)	42	Dapagliflozin, NR	12	NR	NR	67%	NR	NR
Song et al.[18]	United States	Single center, retrospective	50	Empagliflozin (43), canagliflozin (6) dapagliflozin (1)	3.37	57.03	33/17	80%	0.87 (0.33,1.90)	11/39

Abbreviations: KTR, kidney transplant recipients; *N*, number of participants included in the study; NR, not reported; SPKTR, simultaneous pancreas-kidney transplant recipients; UAE, United Arab Emirates.

TABLE 2 Effects of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) on outcomes of interest among kidney transplant patients with diabetes mellitus, comparing levels at baseline and end of the study

		HbA1c (%)		eGFR (ml/min)		Blood pressure (mmHg)		BMI (kg/m^2)	Weight (kg)	
Reference		Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Baseline	Follow up
Kwon and Kong[15]		7.9 ± 1.3	7.4 ± 1.1 at 3 M	71.1 ± 20.1	71.5 ± 25.8 at 12 M	NR	NR	NR	72.2 ± 22.1	68.1 ± 22 at 12 M
Rajasekeran et al.[9]	KTR	8.6 ± 1.4	−0.84 ± 1.2 ($p = .07$)	78 ± 18.2	−4.3 ± 12.2 ($p = .3$)	NR	SBP: −6.5 ± 10.8 ($p = .13$) DBP: −4.8 ± 12 ($p = .3$)	NR	NR	−2.14 ± 2.8 ($p = .07$)
	SPKTR	7.4 ± 1.1		60 ± 14						
Beshyah et al.[16]		8.8	7.8	84	95	115/70	NR	NR	86	78 at 6 M; 84 at 12 M
Schwaiger et al.[8]		6.7 ± 0.7	7.1 ± 0.8 ($p = .03$)	54.0 ± 23.8	53.5 ± 13.3 at 12 M	SBP: 150 ± 26, DBP: 86 ± 14	SBP: 140 ± 20 ($p = .36$) **DBP: 76 ± 11 ($p = .02$)**	29.3 ± 3.1	83.7 ± 7.6	78.7 ± 7.7 ($p = .02$)
AlKindi et al.[10]		9.34 ± 1.36	7.41 ± 1.44 ($p < .05$)	75.75 ± 13.38	69.88 ± 14.70	SBP: 135 ± 9.5, DBP: 80.6 ± 10.1	SBP: 126 ± 11.5 DBP: 74.8 ± 7.3	32.74 ± 7.2	84.8 ± 12.8	82.75 ± 11.35 at 6 M ($p < .05$)
Attallah and Yassine[11]		8.1 ± 0.2	7.1 ± 0.15	95.3 ± 15.97^{+}	97.25 ± 14.84^{+}	NR	SBP: −4.2 at 3 M	26.68 ± 1.0	76.8 ± 7.4	74.94 ± 7.4
Halden et al.[12]	Empagliflozin	6.9 (6.5, 8.2)	6.7 (6.3, 7.5) ($p = .025$)	66 (57, 68)	61 (56, 67)	SBP: 136 (131, 147) DBP: 76 (71, 82)	SBP: 142 (126, 148) DBP: 76 (70, 82)	28.8 (24.7, 39.3)	92.0 (81.8, 104.5)	88.8 (79.0, 100.0) ($p < .014$)
	Placebo	6.8 (6.1, 7.2)	6.9 (6.4, 7.4)	59 (52, 72)	59 (52, 67)	SBP: 135 (127, 146) DBP: 78 (74, 85)	SBP:137 (132, 143) DBP: 80 (74, 86)	27.5 (22.4, 45.8)	84.0 (79.3, 94.0)	85.0 (79.5, 97.5)
Mahling et al.[13]		7.3 (6.4–7.8)	7.1 (6.6–7.5)	57 (47, 73)	NA	SBP: 135, DBP: 80	SBP: −3 (−36, 1), DBP: NR	NR	75	−1 (−1.9, −0.2)
Shah et al.[14]		8.5 ± 1.5	7.6 ± 1.0 ($p < .05$)	86 ± 20[a]	83 ± 18[a]	SBP: 142 ± 21 DBP: 81 ± 9	SBP: 134 ± 17 ($p < .05$) DBP: 79 ± 8	28 ± 3.9	78.6 ± 12.1	76.1 ± 11.2 ($p < .05$)
Kong et al.[17]		7.5 ± 1.1	7.1 ± 1.0 at 6 M ($p = .011$)	60.3 ± 17.0	59.3 ± 14.5	NR	NR	NR	69.6 ± 12.5	68.0 ± 14.0 ($p = .000$)
Song et al.[18]		NR	−0.53 ± 1.79 ($p = .1189$)	66.7 ± 20.6	−1 at 3 M +1 at 6 M	NR	NR	NR	NR	−2.95 ± 3.54 ($p < .001$)

Abbreviations: DBP, diastolic blood pressure; KTR, kidney transplant recipient; M, months; NA, not applicable; NR, not reported; SBP, systolic blood pressure; SPKTR, simultaneous pancreas.
[a]The mean (SD) creatinine clearance; $^{+}$Creatinine.

5 | EFFECT OF SGLT2i ON BODYWEIGHT IN KT PATIENTS

Several glucose-lowering medications, including insulin and sulphonylureas, are associated with weight gain; however, SGLT2i reduce weight within 3 days of starting the medication. Even though the immediate weight loss is most probably related to the natriuretic/diuretic effects of SGLT2i, long-term SGLT2i-induced calorie loss through glycosuria led to 2.0–3.5 kg weight loss in various studies, although this varies considerably between different individuals.[19,29] Similar to SGLT2i studies in non-transplant DM populations, KT patients treated with SGLT2i had a significantly lower weight (mean Δ 2.37 kg) at the end of the included studies compared to their baseline (Table 2). Among 11 studies, the mean weight change at 12 months ranged from −1 kg (Mahling et al.[8]) to −5 kg (Schwaiger et al.[13]). These differences may in part be explained by differences in study design or participant characteristics. Participants in the Mahling study[13] had lower eGFR than in other studies while in the Schwaiger study,[8] participants discontinued all glucose-lowering medications, including insulin, and switched to SGLT2i. Overall, the effects of SGLT2i on weight reduction depends on baseline weight, eGFR, and concomitant medications of subjects. The significant reduction in bodyweight observed in all KT studies mimics results from non-transplant populations and is expected to have favourable effects on cardiovascular health and kidney function of KT patients, as well as improving quality of KT patients' life.

6 | EFFECT OF SGLT2i ON LIPID METABOLISM IN KT PATIENTS

Dyslipidemia is very common in KT patients and is mostly due to the adverse effects of immunosuppressive agents. Dyslipidemia is a major contributor to atherosclerosis which could decrease graft function and patient survival via an increase in cardiovascular events.[30] SGLT2i may increase plasma LDL-cholesterol and HDL-cholesterol and reduce triglyceride levels. The exact mechanism and long-term consequences of an increase in total cholesterol, LDL-cholesterol and HDL-cholesterol are unknown. It has been suggested that these changes can have beneficial cardiovascular effects in the long-term, as SGLT2i reduce the atherogenic small-dense LDL particle levels.[7,31,32] Only two of the 11 studies provided data on changes in lipid levels of KT patients on SGLT2i. Attallah and Yassine reported that LDL-cholesterol increased on average by 5.3 mg/dl and total cholesterol by 4.8 mg/dl with no significant changes in HDL-cholesterol and triglycerides within 12 months.[11] Halden et al. reported significantly higher LDL-cholesterol, HDL-cholesterol, and total cholesterol at the end of 6 months (Table 3).[12] Because dyslipidemia is a common and significant issue in KT patients, future studies should carefully assess the effects of SGLT2i on lipid metabolism in KT patients. Similar increases in LDL cholesterol have been found in the general type 2 diabetes population, where studies demonstrated overall benefit on major adverse cardiovascular events in patients with a history of CVD.

7 | EFFECT OF SGLT2i ON SUA IN KT PATIENTS

SUA levels are often chronically increased in patients with T2DM. Hyperuricaemia is an independent predictor for the development and progression of DKD, atherosclerosis, hypertension and cardiovascular disease in the general population as well as in CKD patients.[33,34] While thiazide or loop diuretics increase SUA levels by reducing uric acid excretion, SGLT2i decrease SUA in patients with T2DM.[7] In KT patients with DM, calcineurin inhibitors may also increase SUA levels.[35] A meta-analysis including 62 randomized control trials (RCT)s with more than 30 000 patients with T2DM, concluded that treatment with a SGLT2i is associated with a significant 0.6–0.8 mg/dl reduction in SUA levels. However, this dramatic reduction was not observed in CKD patients (eGFR<60 ml/min/1.73 m^2).[36,37]

Among the 11 studies evaluated in this review, only three of them reported the effect of SGLT2i on SUA levels. Halden et al. observed a significant median reduction in SUA levels in the empagliflozin group (from 6.72 to 5.49 mg/dl; Δ −0.89 mg/dl) compared to the placebo group (from 6.38 to 6.43 mg/dl; Δ 0.05 mg/dl) at the end of 6 months ($p < .001$).[12] Mahling et al. also reported a 0.2% reduction in SUA levels after 12 months, while Schwaiger et al. reported a significant reduction in SUA levels (from 7.7 to 6.2 mg/dl; Δ −1.5 mg/dl) in 4 weeks ($p = .03$).[8,13] Although there is an association between hyperuricaemia and adverse renal and cardiovascular

TABLE 3 Lipid metabolism outcomes of Halden et al. study presented as median (interquartile range)

	Empagliflozin			Placebo			
Parameter (mmol/L)	Baseline	Week 24	Change	Baseline	Week 24	Change	*p* value
Total cholesterol	4.7 (4.2, 5.1)	4.8 (4.1,5.4)	0.10 (−0.03, 0.3)	4.8	4.3	−0.1 (−0.4,0.0)	<.01
HDL	1.15 (0.9, 1.5)	1.20 (0.9, 1.4)	0.0 (−0.1, 0.1)	1.2 (1.0, 1.5)	1.1 (0.9, 1.3)	−0.1 (−0.1, 0.0	<.05
LDL	2.75 (2.18, 3.2)	2.80 (2.0, 3.1)	0.05 (−0.2,0.3)	2.70 (2.20, 3.1)	2.60 (2.20, 3.0)	−0.1 (−0.3, 0.0)	<.05
Triglycerides	1.80 (1.40, 2.3)	2.05 (1.6, 3.03)	0.20 (0.0, 0.55)	2.0 (1.5, 2.8)	1.9 (1.5, 2.7)	0.0 (−0.3, 0.4)	.103

Note: Variables were analysed per protocol ($n = 44$).
Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein.

outcome in observational studies, recent RCTs CKD-FIX and PEARL concluded that SUA reduction did not prevent the deterioration of kidney functions in CKD patients.[38–40]

8 | EFFECT OF SGLT2i ON BLOOD PRESSURE IN KT PATIENTS

Hypertension is a common comorbidity in KT patients and in T2DM. Use of calcineurin inhibitors is also associated with increased blood pressure. Hypertension is a crucial risk factor for progression of CKD and the development of cardiovascular disease, so strict blood pressure control is central in the management of KT patients. However, blood pressure remains poorly controlled in a large proportion of the general population and in CKD patients.[41,42] Based on 24-h ambulatory blood pressure monitoring studies, SGLT2i reduced systolic and diastolic blood pressure by 4–6 and 1.5–3 mmHg, respectively, without affecting heart rate; this effect is most probably due to natriuresis.[19] While glucosuria related effects (such as glycemic control and bodyweight reduction) are milder when GFR is reduced, natriuresis-related effects of SGLT2i (such as blood pressure reduction) are preserved and even magnified with reduced kidney function, likely due to the increased participation of proximal tubule in sodium reabsorption as eGFR declines.[43] In addition to natriuresis related to inhibition of proximal sodium reabsorption, other factors could also contribute to blood pressure reduction by SGLT2i, such as osmotic diuresis from glycosuria, reduced SUA, improved endothelial dysfunction, and inhibition of the sympathetic nervous system.[7]

Among the 11 studies with KT patients, only seven reported changes in office systolic and diastolic blood pressure (Table 2). No study evaluated ambulatory blood pressure. Schwaiger et al. demonstrated a significant reduction in mean diastolic blood pressure (from 86 ± 14 to 76 ± 11 mmHg, Δ −10 mmHg) with empagliflozin 10 mg/day over 12 months compared to baseline ($p = .02$) while Shah et al. demonstrated a significant reduction in mean systolic blood pressure (from 142 ± 21 to 134 ± 17 mmHg, Δ −8 mmHg) with canagliflozin 100 mg/day over 6 months compared to baseline ($p < .05$).[8,14] Numerical, but not statistically significant reductions in systolic or diastolic blood pressure were also observed in other four studies.[9–11,13]

In contrast, Halden et al. reported an increase in median systolic blood pressure (from 136 to 142 mmHg, Δ +6 mmHg) with empagliflozin 10 mg/day for 6 months; but this was not significantly different from placebo.[12] Of note, several studies in non-KT populations also failed to demonstrate a significant reduction in blood pressure probably because of relatively small sample sizes and lack of standardized study protocols and anti-hypertensive medications. Kong et al. did not observe significant changes in blood pressure, although the number and/or the dose of anti-hypertensive drugs was decreased in 14 out of 39 patients.[17] Therefore, future detailed studies on the effects of SGLT2i on ambulatory blood pressure in KT patients with DM are required to better understand their role in blood pressure optimization in this patient group.

9 | EFFECT OF SGLT2i ON KIDNEY FUNCTION AND PROTEINURIA/ ALBUMINURIA IN KT PATIENTS

Among the 11 studies, 10 reported eGFR changes in KT patients on SGLT2i (Table 2). Importantly, there was no statistically significant change in eGFR with SGLT2i treatment during the follow-up period of each study. The largest numerical reduction in eGFR was reported by AlKindi et al. at −5.87 ml/min/1.73 m^2 within 12 months.[10] The weighted mean difference in changes in eGFR levels of eight studies was −1.9 ml/min/1.73 m^2 when comparing with baseline. The study of Song et al. was not included in the weighted mean difference in changes in eGFR levels because they reported −1 ml/min/1.73 m^2 at 3 months and +1 ml/min/1.73 m^2 at 6 months.[18] Among 11 studies, only Mahling et al. reported an increase in mean eGFR on empagliflozin. However, they provided eGFR values only graphically rather than numerically and the change in eGFR at 12 months was not statistically significant.[13] Shah et al. did not report eGFR but did not observe significant changes in creatinine clearance after 6 month of canagliflozin 100 mg/day.[14] Attallah and Yassine provided serum creatinine rather than eGFR for 8 KT patients followed for 12 months. There was no significant change in serum creatinine while the mean urinary protein to creatinine ratio decreased from 0.95 ± 0.27 g/g at baseline to 0.35 ± 0.13 g/g after 6 months on empagliflozin 25 mg/day.[11] Kong et al. reported no significant change in urine albumin-creatinine ratio in 42 KT patients during 12 months on dapagliflozin, but baseline values were within the normal range (10 mg per gram of urinary creatinine).[17]

Schwaiger et al. reported a significant reduction in eGFR at the end of the first month after the initiation of empagliflozin 10 mg/day, consistent with a functional "dip," as the sequence of eGFR values for 14 patients after SGLT2i initiation was as follows: 54.0 ml/min/1.73 m^2 at baseline, 47.6 at 2 weeks, 45.6 at 4 weeks and 53.5 at 12 months (p value for baseline vs. 4 weeks: .01 while p value for baseline vs. 12 months. .93). The significant initial reduction of 8.4 ml/min/1.73 m^2 in eGFR should be interpreted as an improvement of glomerular hyperfiltration by SGLT2i. There was no significant change in median albuminuria (35 mg/L at the baseline, 53 at 2 weeks, 27 at 4 weeks, 37 at 12 months), a finding that should be interpreted in the context of low baseline albuminuria levels, small sample size and suboptimal method for albumin assessment, as results should be reported in mg/g urinary creatinine or expressed per 24 h.[8] Halden et al. reported a significant increase in median serum cystatin C levels on empagliflozin (from 1.32 to 1.45 mg/L, Δ +0.11) compared to placebo (from 1.44 to 1.40 mg/L, Δ 0) at the end of 6 months ($p < .01$), as well as a significant reduction in eGFR on empagliflozin (Δ −4 ml/min/1.73 m^2 [−7, −1]) compared to placebo (Δ −1 ml/min/1.73 m^2 [−2, 2]) at 8 weeks; however, there was no significant difference in eGFR between empagliflozin and placebo groups.[12] Results from Schwaiger et al. and Halden et al. suggest that the decreases in glomerular hyperfiltration, and, thus, potentially the nephroprotective effect of SGLT2i is also present in KT patients.

This initial "dip" in eGFR observed for SGLT2i resembles the effect of renin-angiotensin system (RAS) blockers – decreasing glomerular hyperfiltration (and eGFR) in the short-term.[22]

These results have potential important implications for KT patients because glomerular hyperfiltration can further reduce their already low nephron mass and graft function, thereby jeopardizing long-term graft survival.[44] Nephroprotection should be confirmed in larger longer-term studies in KT patients. Future studies including a recent RCT (NCT04743453) which includes 220 participants with 1-year follow up of GFR levels will provide more concrete evidence and conclusion for the nephroprotective effects of SGLT2i on KT patients.

10 | SAFETY PROFILE OF SGLT2i IN KT PATIENTS

SGLT2i increase genital yeast infection and urinary tract infections (UTI) due to glucosuria.[45] These adverse events potentially pose a great threat to KT patients who are under immunosuppressive therapy. Moreover, ketoacidosis, and volume depletion, were also reported as adverse events of SGLT2i in T2DM and patients with familial renal glycosuria.[46] Notably SGLT2i did not increase the risk for acute kidney injury in the cardiovascular and kidney trials while ketoacidosis was uncommon in T2DM. Overall long-term safety data for SGLT2i use in KT patients with DM is crucially vital as the current literature does not provide enough outcomes to assess safety profile of SGLT2i in KT patients for long-term.

Among 11 studies, eight studies observed UTI infections in KT patients with DM on SGLT2i (Table 4).[8,10–13,15,17,18] These studies used empagliflozin and dapagliflozin, while Rajasekeran et al.[9] and Shah et al.[14] did not report any UTI events when canagliflozin was used. Rajasekeran et al. reported only one mild hypoglycaemia and cellulitis event, while Shah et al. did not observe any adverse event during the follow-up period of 6 months.[9,14] Whether the different adverse event profiles observed depend on study drug, differences in safety assessments, or short follow up with a small sample group of very selected patients remains unknown. Among 11 studies, Halden et al.[12] and Song et al.[18] reported genital yeast infection and genital

TABLE 4 Safety profiles of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) among kidney transplant patients with diabetes mellitus

Authors	UTI	Genital yeast infection	Hypoglycaemia	Ketoacidosis	AKI	Acute rejection	Other adverse events	Dropped out from the study
Kwon and Kong[15]	2	0	0	0	0	NR		Lack of efficacy (3), Weight loss (1)
Rajasekeran et al.[9]	0	0	1	0	0	0	Cellulitis (1)	
Beshyah et al.[16]	0	0	0	0	0	0		
Schwaiger et al.[8]	3	0	0	0	NR	0		
AlKindi et al.[10]	1	0	0	0	0	NR		
Attallah and Yassine[11]	2	0	0	0	0	0	Nausea (2)	
Halden et al.[12]	3	1	0	0	0	0	Genital itching (1), Dizziness (2), Facial swelling (1), Hematuria (1)	Urosepsis (1)
Mahling et al.[13]	2	NR	NR	0	1	0	Diabetic Ulcer (1)	Tiredness (1), AKI (1)
Shah et al.[14]	0	0	0	0	0	0		Rise in creatinine (1)
Kong et al.[17]	3	NR	NR	NR	NR	NR		UTI (3), Weight loss (2), Preference (3)
Song et al.[18]	7	1	0	0	0	0		UTI (5), genital yeast infection (1), native disease recurrence (1), physician preference (1), resolution of PTDM (1)

Abbreviations: AKI, acute kidney injury; NR, not reported; PTDM, post-transplant diabetes mellitus; UTI, urinary tract infection.

itching in female KT patients on empagliflozin. Among 214 KT patients in 11 studies, 23 UTI and 2 genital yeast infection were reported which indicates a 11.7% cumulative event rate within their relatively short follow-up periods (6–12 months). Even though this rate is similar to other SGLT2i studies with a non-transplant population, the experience so far is insufficient regarding the relative frequency or severity of UTI in KT as compared to the general diabetic population. Only Attallah and Yassine reported that 2 UTI events were observed in female subjects while other studies did not mention the gender of patients who experienced a UTI event.[11]

It is crucial to point out the studies that reported high drop-out rate due to a UTI event. Halden et al. reported one patient with urosepsis as a drop-out besides three patients with at least one UTI event among 22 patients.[12] Moreover, eight patients also dropped out from Kong et al.[17] (3 patients, 7%) and Song et al.[18] (5 patients, 10%) studies due to a UTI event. UTI appeared as the main cause of drop-out in these studies while some other drop-out causes were presented in the Table 4. UTI still possess a serious challenge for the usage of SGLT2i for immunosuppressed KT patients as high drop-out rates due to UTI were reported within short follow-up period by the current literature. Due to the anatomical site of transplanted kidney and immunosuppressant therapies, UTIs possess a great threat to survival of kidney graft and KT patients. Immune-suppressed KT patients, especially those with urinary tract abnormities may be at higher risk of severe or recurrent UTI and this may not have become apparent yet due to very selected patient populations and early withdrawal of SGLT2 if UTI developed. Thus, long-term safety studies with larger KT populations are needed to assess the safety of SGLT2i in KT patients. Future studies including a planned RCT (NCT04906213) which will include 72 KT patient with an 18-month follow up can provide more meaningful evidence for the safety profile of SGLT2i among KT patients.

Among the 11 studies, no study reported ketoacidosis and only Rajasekeran et al. reported one mild hypoglycaemia event. Mahling et al. reported one AKI event while other studies did not report any AKI.[13] No acute rejection episode was reported; however, Shah et al. reported a patient who dropped out of the study due to an insignificant increase in creatinine values.[14] Table 4 presents detailed safety profiles of SGLT2i among KT patients with DM.

11 | INTERACTION WITH IMMUNOSUPPRESSIVE AGENTS

One of the most important aspect of SGLT2i use in KT patients is the potential for drug interactions with immunosuppressive agents. In FDA or EMA assessment documents, no interactions are noted for canagliflozin, dapagliflozin or empagliflozin with transplant-related drugs, although, in general, interactions with immune suppressants were not specifically studied.[47–51] In this regard, pharmacologically, there is no known interaction between empagliflozin and calcineurin inhibitors or mycophenolate.[11] Unfortunately, most studies discussed above did not describe interactions between immunosuppressive and SGLT2i. Halden et al. reported that SGLT2 inhibition did not affect immunosuppressive drug levels.[12] Shah et al. showed that canagliflozin did not alter tacrolimus trough levels and tacrolimus levels (ng/ml) were 6.7 ± 3.7 before and 6.1 ± 2.0, 6 months after starting canagliflozin.[14]

12 | CONCLUSION

Recent large RCTs have confirmed the strong beneficial effects of SGLT2i on cardiovascular health and kidney function and these beneficial effects of SGLT2i could translate into a potential to benefit graft function and survival in KT patients. A review of 11 available studies confirmed the effects of SGLT2i on glycemic control and weight in KT patients with DM although there is a lack of evidence for other effects and immunosuppressive drug interactions due to small sample size and short follow up. So far, the safety profile of SGLT2i in KT patients did not differ from the non-transplant population. However, in addition to the already mentioned small sample size and short duration, evaluation of safety may also be limited by the likelihood of a very selected patient pool. Due to the special risks in KT patients, this is critical before a recommendation for their more widespread use can be made. Thus, larger studies on KT patients with and without DM with a longer follow up are required to confirm the efficacy and safety of SGLT2i in this population. The emphasis in the non-DM population is justified by the demonstration of benefit in general population (non-DM) patients with CKD or heart failure. The first step may be the creation of a multinational multicenter registry to collect information on routine clinical practices for KT patients followed by randomized clinical trials.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Alberto Ortiz, **Atalay Demiray**, **Mehmet Kanbay:** Contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. **Pantelis Sarafidis**, **Mads Hornum**, **Adrian Covic**, **Baris Afsar**, **Alberto Ortiz**, **Mehmet Kanbay:** Drafted the work or revised it critically for important intellectual content. **Peter Rossing**, **Mehmet Kanbay**, **Pantelis Sarafidis**, **Baris Afsar**, **Alberto Ortiz**, **Adrian Covic**, **Atalay Demiray**, **Mads Hornum:** Approved the final version to be published.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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