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Sodium-glucose cotransporter-2 inhibitors (SGLT2i) in kidney transplant recipients: what is the evidence?

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***Abstract*:** Several recent randomized controlled trials (RCTs) have demonstrated the wide clinical application of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in improving kidney and cardiovascular outcomes in patients with native kidney disease. In April 2021, Dapagliflozin became the first SGLT2 inhibitor to be approved by the Food and Drug Administration (FDA) for the treatment of chronic kidney disease (CKD) regardless of diabetic status. However, while these agents have drawn much acclaim for their cardiovascular and nephroprotective effects among patients with native kidney disease, little is known about the safety and efficacy of SGLT2i in the kidney transplant setting. Many of the mechanisms by which SGLT2i exert their benefit stand to prove equally as efficacious or more so among kidney transplant recipients as they have in patients with CKD. However, safety concerns have excluded transplant recipients from all large RCTs, and clinicians and patients alike are left to wonder if the benefits of these amazing drugs outweigh the risks. In this review, we will discuss the known mechanisms SGLT2i exploit to provide their beneficial effects, the potential benefits, and risks of these agents in the context of kidney transplantation, and finally, we will discuss current findings of the published literature for SGLT2i use in kidney transplant recipients and propose potential directions for future research.

Keywords: canagliflozin, dapagliflozin, empagliflozin, kidney transplant, posttransplantation diabetes, sodium glucose cotransporter2

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Introduction

The prevalence of end-stage kidney disease (ESKD) in the United States has increased dramatically in the last few decades and constitutes an incredible burden on the healthcare system.[1] The treatment modality of choice for most patients with ESKD remains kidney transplantation. Kidney transplant recipients (KTRs) experience a higher quality of life and improved long-term survival compared with their waitlisted counterparts on hemodialysis.[2–5] Although patient and allograft survival have improved substantially over the years with advancements in transplant care, cardiovascular disease and infection remain leading causes of mortality in both the early and late posttransplant period.[6–8] Diabetes mellitus (DM) confers significant risk among transplant patients for cardiovascular disease, infectious complications, graft loss, and mortality.[9–11] The disease burden of DM among KTRs is manifold: not only is pre-existing DM the leading cause of native ESKD, constituting the majority of patients on the transplant waiting list and responsible for 31.4% of all kidney transplants in 2019, but also many of the immunosuppressants necessary for successful transplantation pre-dispose KTRs to insulin resistance and beta-cell dysfunction, contributing to the development of diabetes posttransplant.[7,9] Posttransplant diabetes mellitus (PTDM) is a term adopted in 2014 used to describe newly diagnosed diabetes in the posttransplant setting and is found to occur in 10-40% of KTRs.[9,12] Management of diabetes among KTRs is of utmost importance for preventing poor outcomes.

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For the last 20 years, renin–angiotensin–aldosterone blockade agents (ACEi/ARBs) were the only treatment available for managing proteinuric kidney disease in both native and kidney transplant patients. Recently, sodium-glucose transport protein 2 inhibitors (SGLT2i) emerged as a new class of therapeutics with beneficial effects on both cardiovascular (CV) and kidney outcomes in patients with diabetic kidney disease, nondiabetic proteinuric chronic kidney disease (CKD), and heart failure with and without diabetes in patients with native kidneys.[13–21] The possible mechanisms of benefit were extensively investigated and found unlikely to be related to improved glycemic control.[22] On review of these mechanisms, it seems likely SGLT2i may be uniquely beneficial in KTRs with DM, proteinuria, or heart failure to improve allograft longevity and cardiovascular risk. However, SGLT2i therapy is complicated by several factors in KTRs that may limit efficacy or expose patients to unwarranted risk. Reflecting these concerns, all published large, randomized control trials examining the safety and efficacy of SGLT2i have excluded KTRs.[18,23,24] Consequently, there is a dearth of evidence regarding the use of SGLT2 inhibitors in KTRs despite their unique therapeutic promise in this population. There is currently no data on the long-term outcomes of SGLT2i therapy in KTRs including that of overall and CV-related mortality or allograft survival. The very limited evidence in published literature addressing KTRs examine only short-term outcomes and vary dramatically in study design, population characteristics, duration of follow-up and measured outcomes, making it difficult to compare studies or draw meaningful conclusions.[25–33] Here, we will review the proposed mechanisms by which SGLT2i exert their CV and nephroprotective effects in patients with native kidney disease, the potential benefits and concerns of these agents in the context of kidney transplantation and finally we will discuss the findings of the published literature for SGLT2i use in KTRs and propose potential directions for future research.

Proposed mechanisms of SGLT2i efficacy and potential benefits in kidney transplant recipients

Tubuloglomerular feedback and reduction of intraglomerular pressure

SGLT2 inhibitors are blood glucose lowering agents that provide protective benefits to the heart and kidneys to prevent progression of organ failure irrespective of diabetic status in patients with native kidney disease. SGLT2 inhibitors achieve these protective effects through glucose-dependent and glucose-independent mechanisms. In the kidney, SGLT2 inhibitors block sodium and glucose absorption *via* SGLT2 in segment 1 of the proximal tubule, leading to increased sodium, chloride, and glucose delivery to the distal tubule.[22] This increase in sodium and chloride delivery to the distal tubule results in increased tubuloglomerular feedback *via* chloride sensing by the macula densa that causes vasoconstriction of the afferent arterioles resulting in reduction of intraglomerular pressure. Through the reduction of intraglomerular pressure, SGLT2i lower glomerular capillary hypertension and hyperfiltration resulting in reduced physical stress on the filtration barrier, albuminuria, and oxygen demand for tubular reabsorption.[34] This reduction in intraglomerular pressure is evidenced by an acute drop in estimated glomerular filtration rate (eGFR) of about 5 ml/min/1.73m^2 over the first several weeks before returning to baseline and remaining stable.[18,23,35] This hemodynamic effect plays an important role in reducing proteinuria and preserving eGFR in patients with native kidney disease with and without diabetes and may provide substantial benefit for KTRs. Posttransplant proteinuria, both albumin and non-albumin, is highly prevalent and is a major risk factor for early graft loss, major cardiovascular events, PTDM, and all-cause mortality.[36,37] Before SGLT2i, ACEi/ARBs were the only agents available to counteract proteinuria which act by inducing vasodilation of the efferent arteriole to reduce intraglomerular pressure. Although ACEi/ARBs performed well in the nontransplant population, the experience with these agents in KTRs has not been as clear cut. Most clinical trials have shown that while ACEi/ARBs often reduce proteinuria, they do not impart the same benefit on kidney function or graft survival.[36,38] SGLT2i may therefore provide a more effective alternative in KTRs. In addition to reducing proteinuria, SGLT2i-induced reduction in hyperfiltration decreases the metabolic demand for tubular reabsorption and subsequent oxygen consumption.[34] This diminished workload plays an important role in preserving tubular function and eGFR and may be of unique benefit to KTRs, particularly in the setting of deceased donor transplantation and delayed graft function where ischemic tubular injury is common and detrimental to allograft longevity. In summary, SGLT2i

have the potential to reduce proteinuria and preserve eGFR in kidney transplant patients leading to better allograft outcomes.

Glycosuria and metabolic impact

SGLT2 inhibition has been shown to improve metabolic control and function in multiple preclinical and clinical studies employing data from patients with native kidney disease. While SGLT2i induce glycosuria by blocking glucose reabsorption *via* SGLT2, the antihyperglycemic effect of these agents is limited both by more distal glucose absorption in the proximal tubule but also by other metabolic counterregulatory mechanisms that remain intact.[34] In 1 randomized control trial (RCT), empagliflozin reduced glycated hemoglobin (HbA1c) by 0.7% in patients with an eGFR $>$ 60 ml/min/1.73 m^2.[39] Similarly, dapagliflozin only reduced HbA1c between 0.3% and 0.4% in patients with an eGFR $>$ 45 and $\leqslant$60 ml/min/1.73 m^2.[40] The minimal reduction in HbA1c demonstrated in these studies emphasizes that the antihyperglycemic effects of SGLT2i are unlikely to contribute substantially to any protective kidney benefits in patients with advanced CKD. In transplant patients treated with Empagliflozin, the reduction in HbA1c decreased with decreasing eGFR, in line with the decreasing 24-h urinary glucose excretion.[27] However, SGT2i-induced glycosuria can precipitate other beneficial metabolic alterations including shifting substrate utilization from carbohydrate to lipid metabolism.[34] This shift in substrate utilization leads to reduced visceral and subcutaneous fat and subsequently body weight. Lipolysis also releases free fatty acids utilized by the liver to generate ketone bodies, which serves as a more oxygen-efficient fuel. SGLT2 inhibitors thus reduce the work of metabolically active cells like kidney epithelium and cardiomyocytes and prevent long-term injury in these tissues.[41] Indeed, SGLT2i have been shown to increase plasma ketone bodies which has been proffered as a potential mechanism for the cardiovascular benefit.[22] By reducing blood glucose levels and body weight, SGLT2i can also improve beta cell functionality and insulin sensitivity. The metabolic impact of SGLT2i make them particularly attractive for the transplant population who are prone to metabolic dysfunction and development of PTDM secondary to immunosuppressive agents. In addition, posttransplant weight gain and obesity are incredibly common and are associated with a 40% higher risk for death and graft failure.[42] SGLT2 inhibitors may thus play an important role in the prevention or management of diabetes in the transplant setting and may improve metabolic function in KTRs resulting in better patient and allograft outcomes.

Natriuresis and blood pressure control

SGLT2 inhibition also demonstrates a beneficial impact on blood pressure and volume status *via* osmotic diuresis and natriuresis in patients with native kidney disease.[43] This diuretic effect may confer protection against heart failure by improving ventricular load and reducing total body sodium content. A recent study in patients with native kidney disease found that acute SGLT2i treatment increases sodium excretion by 15-20%, an effect which was sustained during chronic treatment and resulted in the reduction of whole-body sodium content.[44] Another RCT showed that empagliflozin monotherapy in patients with type 2 diabetes and stable euvolemic heart failure induced a modest natriuretic effect, an effect which was magnified when used in combination with a loop diuretic.[45] Interestingly, in the same study, they showed that this natriuretic effect was persistent through 14 days, resulting in a reduction in blood and plasma volume. When compared with the traditional loop diuretic bumetanide, dapagliflozin promoted a more sustained natriuresis and subsequent larger reduction in interstitial *versus* intravascular volume.[46] All these studies indicate that SGLT2i function as nontraditional diuretics and improve volume status without activating the renin–angiotensin–aldosterone system (RAAS) in patients with native kidneys.[47] Apart from their effect on volume status, SGLT2i also reduced systolic blood pressure by 4-10 mmHg in both hypertensive and normotensive patients with native kidneys and type 2 diabetes mellitus in multiple RCTs.[48] The antihypertensive action of SGLT2i is most likely due to a combination of osmotic diuresis, weight loss, natriuresis, and an indirect effect on nitric oxide release secondary to better glycemic control.[43] Posttransplant hypertension is highly prevalent, occurring in up to 50-80% of KTRs, and is known to be associated with higher rates of allograft failure.[49] Immunosuppressive agents like calcineurin inhibitors and steroids can induce hypertension through multiple mechanisms such as salt retention, vasoconstriction, and upregulation of RAAS. Improved blood pressure and volume control due to the diuretic effect with SGLT2 inhibitors can therefore play a beneficial role in KTRs with hypertension and volume overload.

Additional diuretic and hematopoietic effects

Given their capacity to induce an osmotic diuresis, SGLT2i can thereby induce urinary excretion of other substrates and electrolytes including uric acid and magnesium in patients with native kidneys.[50] A recent meta-analysis of 62 clinical trials employing data from patients with native kidneys showed that SGLT2i lower and maintain uric acid levels by 35-45 μmol/L.[51] One recent RCT showed that empagliflozin use in patients with native kidneys and type 2 diabetes mellitus, and stable, euvolemic HF was associated with decreased renal magnesium excretion and increased uric acid excretion.[45] Another meta-analysis of 18 RCTs including 15 309 patients with native kidneys found that SGLT2i significantly increased serum magnesium levels compared with placebo.[52] Importantly, however, SGLT2i do not seem to affect potassium handling. A post hoc analysis of the CANVAS trial showed that there were no meaningful effects of canagliflozin on serum potassium levels.[15] Hyperuricemia, hypomagnesemia, and hyperkalemia are all common electrolyte disturbances seen in KTRs; SGLT2i may therefore be beneficial in the management of these electrolyte disturbances.[53,54] SGLT2 inhibition has also been shown to stimulate erythropoietin production. Post hoc analyses from the EMPA-REG OUTCOME trial showed that the rise in hematocrit was associated with cardiovascular protection.[55] However, it was not clear whether the rise in hematocrit was due to volume contraction or due to a primary erythropoietic response. DAPA-HF trial was instrumental in shedding some light on this question as the rise in hematocrit in DAPA-HF was seen after 4 months of treatment.[19] This effectively ruled out the notion that the increased hematocrit response was due to volume contraction. Furthermore, increases in hematocrit were seen irrespective of diabetes status. Recently, human studies further demonstrated the stimulatory effect of empagliflozin and dapagliflozin on erythropoietin production in patients with native kidneys.[56] Anemia is estimated to occur in 30-40% of kidney transplant patients and in known to be a common risk factor for graft loss and mortality in the first 3 years of transplant.[57,58] The etiology of anemia in KTRs is often multifactorial and may include iron deficiency, impaired kidney function, bone marrow suppression secondary to immunosuppression, or antiviral prophylaxis and infection.[57] SGLT2 inhibitors may help in counteracting anemia in KTRs and improve allograft outcomes.

In summary, SGLT2i exert their protective effects through tubuloglomerular feedback and reduced intraglomerular pressure, glycosuria and altered metabolism, natriuresis and blood pressure control, and other additional diuretic and hematopoietic effects reduction which may provide unique benefits to improve cardiorenal outcomes in kidney transplant patients.

Concerns and risks in kidney transplant recipients

As cardiovascular disease and limited allograft survival are both significant challenges facing KTRs, SLGT2 inhibition presents an alluring therapeutic option. However, the use of these agents in this population is complicated not only by the context of a solitary functioning kidney and abnormal genitourinary anatomy but also by the concurrent use of maintenance immunosuppression, high prevalence of immunomodulatory viral infection, and the overall compromised immune state. Infectious risk is therefore of utmost concern and remains a leading cause of mortality, particularly in the early posttransplant period when immunosuppression is at its highest.[59–61] In addition, KTRs have abnormal urogenital anatomy that further predisposes them to develop urinary tract infections (UTIs). UTIs are the most common infectious complication among KTRs, occurring in up to 25% of KTRs in the first year post-transplant and accounting for up to 30% of hospitalizations for sepsis.[62,63] Data from clinical trials in the nontransplant population have shown an increased risk of mycotic genital infections with SGLT2i; post-marketing surveillance data further raised the concern that SGLT2i may predispose patients to necrotizing fasciitis of the perineum, also known as Fournier's gangrene.[64] Fortunately, a recent nested case control study in patients with type 2 diabetes mellitus found there was no increased risk of Fournier's gangrene with SGLT2i use when compared with other antihyperglycemic agents or insulin alone.[65] And while UTIs have not been shown to be associated with SGLT2i therapy in the nontransplant population, the glycosuria induced by SGLT2 inhibition raises concern for KTRs at higher risk for severe urogenital infections including life-threatening urosepsis and Fourier's gangrene.

In addition to the risk of severe urogenital infection, data in nontransplant patients suggest SGLT2i may carry risks for euglycemic ketoacidosis, acute

kidney injury, hypotension, distal limb amputation, or bone fractures.[13,66–70] The risk for many of these adverse effects is already increased in the kidney transplant population. For example, KTRs are at a greatly increased risk of diabetic ketoacidosis and hyperglycemic osmolar syndrome compared with patients with diabetes and with the general population.[71] Despite being preventable, both of these conditions carry a considerable risk of mortality if not optimally treated.[72] Use of SGLT2i therapy has also been avoided in other conditions with increased risk of euglycemic ketoacidosis including T1DM and episodes of acute illness, adding further credence to the hesitation to use these agents in KTRs. In addition, KTRs are exposed to numerous risk factors for hemodynamic ischemic injury in the immediate and early posttransplant period, particularly deceased donor recipients. High prevalence of cardiovascular disease and long-term calcineurin inhibitor therapy are also important contributors to hemodynamic allograft injury even years after transplant. SGLT2i induced afferent arteriolar vasoconstriction and the resultant reduction in intraglomerular pressure may precipitate ischemic injury in a population with an already reduced capacity for autoregulation on calcineurin inhibitors.[18,23,73] Although more recent findings suggest SGLT2i use is not associated with AKI in patients with native kidneys and type 2 diabetes mellitus, generalization of these findings to the transplant population should be made with caution given their unique risk profile.[69,74] It should also be noted that in the immediate posttransplant period, polyuria is exceedingly common and often leads to volume depletion, pre-renal AKI, and hypotension. The natriuretic and diuretic effects of SGLT2i would only serve to compound this issue and would therefore likely be avoided in the weeks following surgery. Other transplant specific concerns that will need to be addressed with SGLT2i use include the potential for attenuated efficacy in the setting of a solitary, denervated kidney, as well as the potential for drug interactions and the effects on immunosuppression levels.

SGLT2 inhibition in chronic kidney disease in patients with native kidneys

SGLT2 inhibitors have demonstrated cardiorenal benefits in patients with CKD. A systematic review and meta-analysis of 27 studies with up to 7363 participants showed that SGLT2i reduce the risk of cardiovascular and kidney outcomes in patients with type 2 diabetes mellitus and CKD, without clear evidence of safety concerns.[75] Similarly, a recent meta-analysis of 9 RCTs, comprising 60,914 patients, showed decreased kidney disease and CKD progression in patients with type 2 diabetes mellitus and CKD.[76] The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was the first RCT that examined the impact of SGLT2i on the clinically important kidney outcomes in individuals with type 2 diabetes mellitus, CKD, and macroalbuminuria.[24] CREDENCE enrolled 4401 individuals with an eGFR of 30-90 ml/min/1.73 m^2 and macroalbuminuria (urine albumin to creatinine ratio >300 mg/g). These individuals were on maximally tolerated doses of ACEi/ARBs. Over 2.62 years of follow-up, compared with placebo, canagliflozin 100 mg/day reduced the primary composite outcome of ESKD, serum creatinine doubling, or death from cardiovascular or kidney disease by 30%. More recently, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial examined the use of dapagliflozin 10 mg/day, in addition to ACEi/ARBs in CKD patients with and without diabetes.[77] DAPA-CKD enrolled 4304 CKD patients with an eGFR from 25-75 ml/min/1.73 m^2 and urine albumin to creatinine ratio between 200 and 5000 mg/g. Of the total number of patients, 32.5% did not have diabetes. The primary outcome of interest was a 50% decline in eGFR, new onset ESKD, or death from kidney or cardiovascular causes. Over a median follow-up of 2.4 years, dapagliflozin 10 mg/day compared with placebo reduced the primary outcome by 49%. The effects of dapagliflozin were similar in participants with and without type 2 diabetes. Apart from these two-kidney focused RCTs, other major cardiovascular trials showed similar renal outcomes in the secondary analyses.[78] In terms of cardiovascular benefit, SGLT2i have been shown to reduce hospitalization of heart failure, cardiovascular death, and myocardial infarction according to a recent meta-analysis of 6 outcome trials.[79] Unfortunately, none of these RCTs enrolled patients who had received a kidney transplant due to safety concerns, resulting in the current dearth of evidence regarding the utilization of SGLT2i in KTRs. Extrapolating from the cardiovascular and kidney benefits observed in other populations, these agents hold much potential to preserve allograft function and reduce the considerable cardiovascular disease burden in KTRs.

Current evidence in kidney transplant recipients

The available evidence on the safety and efficacy of SGLT2i therapy in KTRs is very limited, encompassing only 9 published studies to date (October 2021), consisting of 8 manuscripts and 1 abstract including 182 patients from 8 countries, which are summarized in Table 1.[25–33] Of the listed studies, only 1 was a randomized control trial by Halden *et al.*,[27] which consisted of 22 patients in both the treatment arm and placebo arm. The remaining studies were case series and cohort studies.[27] A recent meta-analysis by Chewcharat *et al.*[80] included all the listed studies, except for Song *et al.*, which was published after the meta-analysis was conducted. In this meta-analysis, the mean age of participants ranged from 46-66 years old and the baseline eGFR among all participants was 64.5 ± 19.9 ml/min/1.73 m^2.[80] Most of the listed studies assessed SGLT2i therapy in stable KTRs with preexisting DM or PTDM that were many years posttransplant; time from transplant to SGLT2i initiation ranged from 3-20 years.[80] One study by Song *et al.*[32] sought to evaluate the safety and efficacy of early initiation of SGLT2i within the first year of transplant when the risk of AKI and UTI is presumed to be highest due to labile allograft function and more potent immunosuppression. The average time from transplant to SGLT2i initiation in this study was 319.5 days.[32] All studies had a follow-up duration of less than 1 year.[32,80] Given the limited follow-up, these studies focused predominantly on short-term outcomes, notably glycemic control, body weight reduction, eGFR, and blood pressure (BP) changes, along with safety data (Table 2).[32,80] Long-term outcomes on chronic allograft function, cardiovascular morbidity and mortality, as well as graft and patient survival remain to be explored.

Effects on kidney allograft function and proteinuria/albuminuria

As stated previously, the currently available data in KTRs are insufficient to comment on the long-term cardiovascular or kidney outcomes of SGLT2i therapy. That said, there is reassuring evidence that the some of the same mechanisms which impart cardiorenal benefit in the nontransplant population are also present in KTRs, most notably, the physiologic early dip in eGFR in response to SGLT2i initiation.[27,30] As described earlier, an early acute drop in eGFR followed by stabilization is consistent with an intact hemodynamic response induced by restored tubuloglomerular feedback. It therefore stands to reason that if this early eGFR 'dip' is present in KTRs, then the long-term benefits of reduced hyperfiltration are likely to ensue. Halden *et al.*[27] and Schwaiger *et al.*[30] demonstrated that this early eGFR response is present in kidney transplant patients. The mean eGFR reported by Schwaiger *et al.*[30] dropped from a baseline of 54.0 ml/min/1.73 m^2 to 45.6 ml/min/1.73 m^2 at 4 weeks (Δ8.4 ml/min/1.73 m^2; $p = 0.01$) and then improved to 53.5 ml/min/1.73 m^2 by month 12 (Δ0.5 ml/min/1.73 m^2; $p = 0.93$; compared with baseline) in KTRs on empagliflozin. Similarly, Halden *et al.*[27] reported a significant reduction in eGFR (–4 ml/min/1.73 m^2) 8 weeks after SGLTi initiation compared with placebo ($p < 0.05$) but not at week 24 (Δ0 ml/min/1.73 m^2; $p = 0.61$). The presence of this eGFR 'dip' is particularly interesting given that the transplanted kidney is essentially denervated, and as such, is not responsive to sympathetic output which may blunt an autonomic-induced hemodynamic response. This suggests that SGLT2i may be more effective in preserving allograft function than ACE inhibition which works in part by reducing renal sympathetic output. It is important to note that SGLT2i trials in nontransplant patients were conducted in combination with ACEi/ARB therapy; however, RAAS blockade was not consistently reported in studies in KTRs. Although current data have not shown a significant difference in kidney outcomes such as eGFR, serum creatinine, urine protein, or urine microalbumin in KTRs on SGLT2i, it is necessary to keep in mind that the short duration of follow-up in these studies was not adequate to capture the long-term benefits of these agents.[32,80] Furthermore, the early drop in eGFR observed in a few of the studies is reassuring that SGLT2i act similarly in KTRs as they do in the nontransplant population and will likely demonstrate similar cardiorenal benefits with longer follow-up.

Effects on glycemic control, body weight, blood pressure, and serum uric acid levels

Consistent with literature in the nontransplant population, SGLT2i use in KTRs is associated with a modest reduction in HbA1c. A recent meta-analysis by Chewcharat *et al.*[80] found that in 8 studies with 132 participants, SGLT2i use significantly lowered mean HbA1c by 0.57% at the end of the study compared with baseline (95%CI:

Table 1. Studies of sodium-glucose co-transporter type 2 inhibitors (SGLT2i) in kidney transplant recipients.

Author, year	Study Type	N	Drug with dose (n)	Follow-up (months)	% DM prior to KT	Inclusion criteria	Exclusion criteria
Halden *et al.*, 2019[27]	RCT	Empaligflozin (n = 22) Placebo (n = 22)	Empagliflozin 10 mg	6	0%	1. Age ⩾ 18 KT ⩾ 1 year prior 2. Stable kidney function (<20% deviation in SCr in 2 months) 3. Stable IS therapy for 3 months	1. eGFR < 30 ml/min/1.73 m2 2. Pregnant or lactating women
Schwaiger *et al.*, 2019[30]	PS	14	Empagliflozin 10 mg	12	0%	1. Age ⩾ 18 2. KT ⩾ 6 months 3. eGFR ⩾ 30 ml/min/1.73 m^2 4. PTDM treated > 6 months	1. Insulin therapy ⩾ 40 IU/day 2. HbA1c ⩾ 8.5%
Mahling *et al.*, 2019[28]	CS	10	Empagliflozin	12	60%	1. Stable allograft function 2. eGFR > 45 ml/min/1.73 m^2 3. No history of UTI	1. T1DM 2. History of UTI
Attallah and Yassine, 2019[26]	CS	8	Empagliflozin 25 mg/day	12	50%	–	–
Rajasekeran *et al.*, 2017[29]	CS	10	Canagliflozin	8	20%	1. Adult's s/p KT or KPT	–
Shah *et al.*, 2019[31]	PS	24	Canagliflozin 100 mg	6	83%	1. Age ⩾ 18 years 2. Stable kidney function 3. Cr clearance > 60 ml/min HbA1c > 6.5%	1. Unstable Cr 2. Cr clearance < 60 ml/min 3. Total bilirubin > 1.5× normal 4. ALT > 2× normal 5. Recent UTI or genital mycosis
Kong *et al.*, 2019[33]	PS	42	Dapagliflozin 5 mg/day	12	67%	–	–
AlKindi *et al.*, 2020[25]	CS	8	Empagliflozin 10 mg/day (5), Empagliflozin 25 mg/day (1), Dapagliflozin 5 mg/day (2)	12	25%	–	–
Song *et al.*, 2021[32]	RS	50	Empagliflozin (43), Canagliflozin (6), Dapagliflozin (1)	6	80%	1. T2DM or PTDM 2. No AKI ⩽ 30 days prior 3. No UTIs ⩽ 6 months prior 4. eGFR ⩾ 30 ml/min/1.73 m^2	–

ALT, alanine transferase; CS, case series; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; KT kidney transplant; KPT, kidney and pancreas transplant; PS, prospective study; PTDM, posttransplant diabetes mellitus; RCT, randomized controlled trial; SCr, serum creatinine; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

Table 2. Outcomes and safety profile of sodium-glucose co-transporter type 2 inhibitors (SGLT2i) in kidney transplant recipients with diabetes mellitus.

Author, year	Study Type	Change in baseline metabolic parameters		Change in baseline kidney parameters		Adverse effects in SGLT2i group	Dropped out from study
Halden *et al.*, 2019[27]	RCT	Median (IQR) 1. ΔHgAlc −0.2 (−0.6 to −0.1) *versus* 0.1 (−0.1 to 0.4) 2. ΔFPG −0.65 (−1.2 to −0.13) *versus* 0.30 (−0.45 to 0.55) mmol 3. Δ2 h PG −1.75 (−3.7 to 0.93) *versus* -0.40 (−1.4 to 1.4) mmol/L 4. ΔBody weight −2.5 (−4 to −0.05) *versus* 1.0 (0.0 to 2.0) kg	$p = 0.025$ $p = 0.272$ $p = 1.0$ $p = 0.014$	Median (IQR) 1. ΔeGFR −3 (−7 to 0) *versus* −1.0 (−2.8 to 0.75) 2. ΔSBP −5 (−12 to 1) *versus* 2 (−6 to 8) mmHg	$p = 1.0$ $p = 0.06$	UTI (n = 3) Genital yeast infection (n = 1)	Urosepsis (n = 1)
Schwaiger *et al.*, 2019[30]	PS	Mean (+ SD) 1. ΔHbA1c 6.7 (±0.7) inc. to 7.1 (+0.8)% 2. ΔFPG inc. to 144 ± 45 mg/dl 3. Δ2-h PG inc. to 273 ± 116 mg/dl 4. ΔBody weight 83.7 ± 7.6 to 78.7 ± 7.7 kg 5. ΔSBP 150 (26) to 145 (20), $p = 0.36$	$p = 0.03$ $p = 0.005$ $p = 0.06$ $p = 0.02$	Mean (+ SD) 1. ΔeGFR 54.0 ± 23.8 to 53.5 ± 13.3 Median (IQR) 1. ΔUPCR 206 (84-901) to 348 (147-555) mg/g	$p = 0.93$ $p = 1.0$	UTI (n = 5) Balanitis (n = 1) Pneumonia (n = 1)	
Mahling *et al.*, 2019[28]	CS	Median (IQR) 1. ΔHbA1c 7.3 (6.4-7.8) to 7.1 (6.6-7.5) 2. ΔBody weight −1 (−1.9 to -0.2) kg 3. ΔSBP −3(−36 to 1) mmHg	-	Urine protein not recorded	-	UTI (n = 2) AKI (n = 1) Diabetic ulcer (n = 1)	Tiredness(n = 1) AKI(n = 1)
Attallah and Yassine, 2019[26]	CS	Mean 1. ΔHbA1c −0.85 g/dl 2. ΔBodyweight −2.4 kg/year 3. ΔSBP −4.2 mmHg	-	Mean ΔUrine protein −0.6 g/day	-	UTI (n = 2) Nausea (n = 2)	
Rajasekeran *et al.*, 2017[29]	CS	Mean (± SD) 1. ΔHbA1c −0.84 ± 1.2% 2. ΔBody weight −2.14 ± 2.8 kg	$p = 0.07$ $p = 0.07$	Mean (+ SD) 1. ΔeGFR −4.3 ± 12.2	$p = 0.3$	Cellulitis (n = 1) Hypoglycemia (n = 1)	
Shah *et al.*, 2019[31]	PS	Mean (± SD) 1. ΔHbA1c 8.5 ± 1.5% to 7.6 ± 1% 2. ΔBody weight 78.6 ± 12.1 kg to 76.1 ± 11.2 kg 3. ΔBP 142 ± 21 and 81 ± 9 to 134 ± 17 and 79 ± 8 mmHg 4. ΔTacrolimus level 6.7 ± 3.7 ng/ml to 6.1 ± 2 ng/ml	$p < 0.05$ $p < 0.05$ (SBP)	Mean (± SD) 1. ΔSCr 1.1 ± 0.2 before and 1.1 ± 0.3 after	-	None reported	Rise in creatinine(n = 1)
Kong *et al.*, 2019[33]	PS	Mean (± SD) 1. ΔHbA1c 7.5 ± 1.1% to 6.9 ± 0.8%% 2. ΔBody weight 69.6 ± 12.5 to 68.0 ± 14.0 kg	$p = 0.000$	Mean (± SD) 1. ΔeGFR 60.3 ± 17.0 to 59.3 ± 14.5 ml/min/1.73 m^2	–	Acute cystitis (n = 2)	UTI(n = 3) Weight loss (n = 2) Physician preference (n = 1)
AlKindi *et al.*, 2020[25]	CS	Mean (± SD) 1. ΔHbA1c 7.41 ± 1.44 from 9.34 ± 1.36 2. ΔSBP 126.43 ± 11.46 from 135 ± 9.59 3. ΔBMI 27.4 ± 4.2 from 32.74 ± 7.2	$p < 0.05$ $p < 0.05$ $p < 0.05$	Mean (± SD) 1. ΔeGFR 69.88 ± 14.70 from 75.75 ± 13.38 ml/min/1.73 m^2	$p < 0.05$	UTI (n = 1)	
Song *et al.*, 2021[32]	RS	Mean (± SD) 1. ΔHbA1c −0.53% (±1.79) 2. ΔWeight −2.95 kg (±3.54)	$p = 0.1189$ $p < 0.0001$	Mean (± SD) 1. ΔeGFR + 1 ml/min/1.73 m^2	$p = 0.1478$	UTI (n = 7) Genital mycosis (n = 1)	UTI (n = 5) Genital yeast infection (n = 1) Native disease recurrence (n = 1) Physician preference (n = 1) Resolution of PTDM (n = 1)

CS, case series; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PG, plasma glucose; PS, prospective study; RCT, randomized controlled trial; SBP, systolic blood pressure; SCr, serum creatinine; UTI, urinary tract infection; UPCR, urine protein creatinine ratio.

–0.97,–0.16; $p = 0.006$, $I^2 = 85.2\%$); in the 5 studies with 12-month follow-up data in 76 participants, SGLT2i use lowered mean HbA1c similarly by 0.58% (95% CI: –1.12, –0.05; $p = 0.03$, $I^2 = 79.8\%$). However, a shorter duration of follow-up at 6 months was not associated with a statistically significant difference in HbA1c.[27,31–33,80] The largest reductions in mean HbA1c (0.8-1.9%) were observed in the studies with higher baseline mean HbA1c.[25,26,29,31] One noninferiority study by Schwaiger *et al.*[30] comparing low dose insulin therapy with empagliflozin demonstrated empagliflozin monotherapy was associated with a rise in mean HbA1c of +0.4% and worse oral glucose tolerance test indices. This suggests that SGLT2i agents should be used in combination with other anti-hyperglycemic agents and not as monotherapy. Supporting this, the study by Song *et al.*[32] showed that overall insulin usage declined by –3.7 units, though did not reach statistical significance. Overall, the effects of SGLT2i on glycemic control in KTRs with DM are comparable with the modest reduction demonstrated in the nontransplant population.

SGLT2i therapy also demonstrated a consistent reduction in body weight in all studies. In the 88 studies included in the meta-analysis by Chewcharat, SGLT2i use was associated with a significant decrease in both body mass index and body weight at 6 months with a weight mean difference of –0.8 kg/m^2 ($p = 0.007$) and –2.49 kg ($p = 0.003$), respectively. However, in the 3 studies with 12-month follow-up data, only body weight remained significantly reduced by an average of –1.97 kg (95%CI:–3.21, –0.73; $p = 0.002$, $I^2 = 0\%$).81[80] Similarly, the retrospective study by Song *et al.*[32] showed a statistically significant reduction in body weight by –2.95 kg ($p < 0.0001$). The reduction in mean body weight varied between studies likely due to differences in baseline weight, eGFR, study design, and concomitant medications and ranged from –1 kg in Mahling *et al.* to –5 kg in Schwaiger *et al.*[28,30] As body weight reduction induced by SGLT2i may be consequent to natriuresis and total body water loss or to glycosuria and caloric loss, a few studies went further to delineate the cause of body weight reduction. Halden *et al.*[27] showed there was no difference in fat mass with SGLT2i use as measured with a modified DXA technique. However, Schwaiger *et al.*[30] demonstrated a significant reduction in total body water as measured by bioimpedance. More trials with longer follow-up will help to further delineate the contribution of SGLT2i to reduction in total body water and fat mass.

While body weight was consistently reduced, however, blood pressure was not shown to be significantly affected by SGLT2i therapy. In the 6 studies that measured blood pressure in the meta-analysis, SGLT2i failed to demonstrate significant reduction in either systolic or diastolic blood pressure.[80] Of these studies, one showed significant reduction in systolic blood pressure by 8 mmHg in 12 months compared with baseline ($p = 0.02$) though failed to demonstrate a significant reduction in diastolic blood pressure.[31] Another demonstrated significant reduction in diastolic blood pressure by 10 mmHg in 6 months compared with baseline ($p < 0.05$), but failed to show a difference in systolic blood pressure.[30] While not shown to be statistically significant, most studies showed a trend toward reduced blood pressure when compared with baseline. The nonsignificant findings are therefore more likely a reflection of the small study sizes, limited study designs, and insufficient power to detect a statistically significant difference. Larger randomized controlled trials are likely to demonstrate a modest reduction in blood pressure similar to that observed in nontransplant patients.[81] It should be noted that in all studies, the reported blood pressures were measured on clinic visits and were not collected by more accurate ambulatory blood pressure monitoring. Future studies should consider ambulatory blood pressure monitoring for improved accuracy.

Out of the 9 listed studies in KTRs, only 3 studies reported changes in serum uric acid levels.[27,28,30] In the only RCT, Halden *et al.*[27] demonstrated treatment with empagliflozin was associated with a significant median reduction in serum uric acid level by –53 μmol/L ($p < 0.001$) at 6 months when compared with placebo. Schwaiger *et al.*[30] also reported a significant reduction in serum uric acid of –1.5 mg/dl at 4 weeks compared with baseline ($p = 0.03$), though this effect was not statistically significant at 12 months ($p = 0.08$), perhaps on the account of patient drop out. Mahling *et al.*[28] similarly showed a 0.2% reduction in serum uric acid level. Larger studies in KTRs will be needed before any conclusions may be drawn from either the effect of SGLT2i inhibitors on serum uric acid levels or the relative contribution of reduced serum uric acid levels on the long-term cardiorenal

benefits of SGLT2i in KTRs. Regarding the effects of SGLT2i on magnesium levels in KTRs, only 1 study reported serum magnesium levels. Interestingly, Song *et al.*[32] found that SGLT2i are associated with a significant decrease of 0.13 mg/dl in serum magnesium levels compared with baseline ($p = 0.0004$). This is inconsistent with findings in other populations and will need to be replicated in prospective RCTs before further comment can be made. In addition, 3 studies also observed an increase in hematocrit consistent with nontransplant studies.[27–29]

Safety and adverse effects

Before widespread use of SGLT2i can be recommended for KTRs, their safety profile in this population must be firmly established. Adverse events in the 9 listed studies are summarized in Table 2. The most common reported adverse effect in the available studies in KTRs is UTI. Among the 9 published studies, UTI was reported in 21 out of 182 patients, or a cumulative event rate of 11.5%, consistent with previously reported incidence rates of UTIs among KTRs.[32,80,82] Two genital mycotic infections were also reported, 1 by Halden *et al.*[27] and 1 by Song *et al.*[32] There were no reported incidences of Fourier's gangrene. However, it is important to note that many studies also reported high dropout rates due to UTI which were not included in the above event rate.[27,32,33] In addition to the 3 reported UTIs in the empagliflozin arm, Halden *et al.*[27] also reported 1 patient who had to drop out of the study due to urosepsis, though that patient had experienced similar episodes of urosepsis prior to inclusion in the study. Kong *et al.* and Song *et al.* also reported a total of 8 patients, 3 (7%) and 5 (10%) respectively, who dropped out due to episodes of UTI. There was also 1 patient who dropped out of the Song *et al.*[32] study due to genital mycotic infection and 1 patient from Halden *et al.*[27] who dropped out due to genital itching. It should also be recognized that many of these studies excluded patients with a prior history of recurrent UTI or a history of UTI in the 6 months prior to SGLT2i initiation.[27,28,31] All of the studies except Song *et al.*[32] also evaluated KTRs that were many years posttransplant and therefore at lower risk of infectious complications.[80] Although the reported cumulative incidence rates appear similar to those of the general KTR population, the current data are insufficient to determine the relative frequency or severity of SGLT2i-associated urogenital infections among KTRs given the relatively high dropout rates and limited sample size. As such, the risk of urogenital infection still poses a substantial challenge for SGLT2i utilization in KTRs.

Other reported adverse events include 1 episode of AKI and 1 diabetic ulcer reported by Mahling *et al.*[28] and 1 episode of cellulitis reported by Rajasekeran *et al.*[29] Other causes for patient dropout included 1 patient with AKI from Mahling *et al.*, 1 patient with a rise in creatinine from Shah *et al.*, 2 patients with weight loss from Kong *et al.*, 1 patient with native disease recurrence from Song *et al.*, 1 patient with resolution of PTDM from Song *et al.*, 3 patients due to patient preference in Kong *et al.*, and 1 patient due to physician preference in Song *et al.*[28] There were no reported incidences of ketoacidosis, hypotension, distal limb amputations, or bone fractures.

Another important aspect of SGLT2i utilization in KTRs is the potential for drug interactions, particularly SGLT2i effects on immunosuppression levels. Although primarily metabolized through O-glucuronidation, SGLT2i is also metabolized through the CYP3A4 pathway, the same utilized by calcineurin inhibitors.[83,84] Although no interactions of SGLT2i with calcineurin inhibitors and mycophenolate have been reported in the literature, there have been no studies evaluating these interactions specifically. Unfortunately, only 2 of the listed studies reported immunosuppressive drug levels. Halden *et al.*[27] reported no changes in tacrolimus, cyclosporine or everolimus trough levels with empagliflozin and Shah *et al.*[31] reported no changes in tacrolimus trough levels with canagliflozin.

Conclusion

Although the data are currently very limited, SGLT2i utilization in KTRs has demonstrated a modest effect on improving glycemic control, body weight, and serum uric acid levels consistent with findings in the nontransplant population. Although there was a trend toward blood pressure reduction with SGLT2i therapy, this did not meet statistical significance when evaluated by meta-analysis, likely due to limited sample size, varied patient characteristics, and study design.[80] Although the potential cardiorenal benefits of SGLT2i therapy have not been substantiated yet in KTRs, there is reassuring evidence of a physiologic dip in eGFR consistent with an appropriate hemodynamic

response and reduction in hyperfiltration which remains intact in KTRs and is likely to translate to long-term benefit. The frequency of reported adverse effects in KTRs does not appear to exceed those found in nontransplant patients or in KTRs in the absence of SGLT2i therapy. However, as mentioned earlier, the current data are very limited and large trial data will be needed before SGLT2i therapy can be safely recommended in this population. Larger RCTs with longer follow-up are also desperately needed to evaluate the long-term cardiovascular and kidney outcomes of SGLT2i therapy in the transplant setting.

Author contributions

Aditi Ujjawal: Data curation; Methodology; Writing – original draft; Writing – review & editing.

Brittany Schreiber: Data curation; Methodology; Writing – original draft; Writing – review & editing.

Ashish Verma: Conceptualization; Data curation; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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