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RESPONSIBLE EDITORS FOR THIS ISSUE

Sodium-glucose cotransporter-2 inhibitor use in kidney transplant recipients

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are novel oral hypoglycemic agents garnering much attention for their substantial benefits. These recent data have positioned SGLT2i at the forefront of diabetic chronic kidney disease (CKD) and heart failure management. SGLT2i use post-kidney transplant is an emerging area of research. Highlights from this mini review include the following: Empagliflozin is the most prescribed SGLT2i in kidney transplant recipients (KTRs), median time from transplant to initiation was 3 years (range: 0.88-9.6 years). Median baseline estimated glomerular filtration rate (eGFR) was 66.7 mL/min/1.73 m² (range: 50.4-75.8). Median glycohemoglobin (HgbA1c) at initiation was 7.7% (range: 6.9-9.3). SGLT2i were demonstrated to be effective short-term impacting HgbA1c, eGFR, hemoglobin/hematocrit, serum uric acid, and serum magnesium levels. They are shown to be safe in KTRs with low rates of infections, hypoglycemia, euglycemic diabetic ketoacidosis, and stable tacrolimus levels. More data is needed to demonstrate long-term outcomes. SGLT2i appear to be safe, effective medications for select KTRs. Our present literature, though limited, is founded on precedent robust research in CKD patients with diabetes. Concurrent research/utilization of SGLT2i is vital to not only identify long-term patient, graft and cardiovascular outcomes of these agents, but also to augment management in KTRs.

Key Words: Sodium glucose cotransporter-2; Sodium glucose cotransporter-2 inhibitor; Kidney transplantation; Diabetes; Post-transplant diabetes mellitus; New onset diabetes after transplant

Core Tip: Multiple large trials have demonstrated sodium-glucose cotransporter-2 inhibitors (SGLT2i) associated kidney and cardiovascular benefits for chronic kidney disease patients with diabetes. Important considerations are critical to determine safety and efficacy of these medications after kidney transplantation. While evidence is limited, SGLT2i appear to be both safe and effective short-term. More robust research is needed to determine the long-term impacts of their use in kidney transplant recipients. Appropriate patient selection and monitoring are vital to clinical use and future research efforts of SGLT2i in kidney transplantation.

INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) or "gliflozins", are oral hypoglycemics that work by inducing glucosuria. They are derived from phlorizin, a glucosuric compound found in apple tree root bark. As described by van Bommel *et al*[1], there are 2 clinically significant sodium-glucose transporters found in humans: SGLT1 Low-affinity high-capacity transport in the distal convoluted tubule and SGLT1 high-affinity low-capacity transporter in proximal convoluted tubule. As noted by Salvatore *et al*[2] and Sawaf *et al*[3], SGLT2i reduces the glucose excretion threshold to 2.2 mmol/L (40 mg/dL) from 10 mmol/L (180 mg/dL).Consequently, they have been shown to reduce glycohemoglobin (HgbA1c) by 0.6%-0.9% with glomerular filtration rate (GFR) > 60 mL/min and 0.3%-0.4% with GFR 30-59 mL/min[1]. SGLT2i also block the sodium/glucose symport channel in the proximal convoluted tubule leading to osmotic diuresis and natriuresis[3]. This excess sodium excretion is thought to induce afferent vasoconstriction through glomerular feedback thereby reducing hyperfiltration[1].

Data on SGLT2i have demonstrated great promise for their use in chronic kidney disease (CKD) patients with diabetes. In a recent meta-analysis, Zelniker *et al*[4] synthesized the findings of multiple landmark trials (EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI). They showed that SGLT2i reduced the risk of renal disease progression by 45% [hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.48-0.64, $P < 0.0001$], and cardiovascular death or heart failure hospital-ization by 23% (HR = 0.77, 95%CI: 0.71-0.84, $P < 0.0001$) in patients with and without atherosclerotic heart disease.

These renoprotective benefits have been observed in patients with, as well as without, diabetes. Heerspink *et al*[5], *via* dapagliflozin (DAPA)-CKD, showed that DAPA in CKD patients with or without diabetes reduced the risk of a composite outcome of estimated GFR (eGFR) decline of at least 50%, end stage kidney disease (ESKD), or death from renal/cardiovascular cause (HR = 0.56, 95%CI: 0.45-0.68, $P < 0.001$) with a number needed to treat of 19 (95%CI: 15-27).

As shown by adoption of SGLT2i as first line therapies for CKD patients with diabetes by the 2022 Kidney Disease Improving Global Outcomes guidelines by Rossing *et al*[6], evidence for these agents is promising. Favorable outcomes owing to SGLT2is have led the transplant community to investigate their broader application.

Many dependent diabetic kidney transplant recipients (KTR) appear to be likely beneficiaries of SGLT2i therapy. As described by Chewcharat *et al*[7], 40% of waitlisted patients have diabetes mellitus (DM) and 15%-30% of non-diabetic patients develop post-transplant DM (PTDM)[7]. PTDM is associated with high rates of graft loss, cardiovascular disease, infectious complications, and mortality[7]. Inherent risks of kidney transplantation *e.g.,* urinary tract infection, concern for drug interactions *i.e.,* immunosuppression, and acute kidney injury/CKD risk, have raised safety and efficacy concerns of SGLT2i.

In this mini review, we aim to summarize recent literature describing SGLT2i usage in KTRs to: (1) Provide guidance for clinical use; (2) identify current limitations; and (3) highlight future directions. We hope this mini review will act as a reference for clinicians and researchers alike to advance clinical/translational research and characterize SGLT2i's role in diabetes management after kidney transplantation.

SEARCH STRATEGY

We conducted literature searches in PubMed, Cochrane, Google Scholar from January 2019 to January 2023 and reference lists of relevant studies and reviews. Key words utilized in our search included the following: "SGLT2 inhibitors, SGLT2i, KTRs, type 2 diabetes mellitus, post-transplant diabetes mellitus."

We limited our search to studies with available full text and English language. In this mini review, we selected studies of SGLT2i use in type 2 DM (T2DM) and/or PTDM in KTRs that were either: (1) Prospective randomized control trials; (2) prospective case series; and/or (3) retrospective case series with comparison groups. We limited study inclusion to those occurring in the last 4 years to highlight recent research.

For our analysis of the following outcomes: HgbA1c, eGFR, weight, blood pressure, Immunosuppression drug interactions, adverse events, we pooled studies that reported these data together. As descriptions of cost, novel findings, and long-term outcomes were limited to one or a few studies, these were simply discussed in context of specific studies.

Nine studies met our search criteria: 1 randomized controlled trial, 2 prospective observational studies, and 5 retrospective analyses, of which 2 had comparison groups. All nine studies occurred in the last 4 years.

FINDINGS

In this sample, empagliflozin (*n* = 241) was the most prescribed SGLT2i followed by DAPA (*n* = 85) and canagliflozin (*n* = 74). The median time from transplant for initiating SGLT2i was 3 years (range: 0.88-9.6 years post-transplant). Median baseline eGFR was 66.7 mL/min/1.73 m² (range: 50.4-75.8). Median HgbA1c at initiation was 7.7% (range: 6.9-9.3). The following results were seen and are summarized in Table 1.

HgbA1c

HgbA1c generally improved with changes between 0.2%-1% in the reported studies. Notably, in the study by AlKindi *et al*[8], which included a cohort with a mean HgbA1c of 9.3% at initiation as well as excellent allograft function, HgbA1c decreased by 2.3% at 12 mo. As is described by Halden *et al*[9], more robust impacts on glycemic control were observed in those with higher HgbA1c and eGFR.

eGFR

eGFR was preserved in most studies over a period of 6-12 mo[8-13]. Lim *et al*[13] observed a 10% eGFR dip in 15.6% of their cohort with SGLT2i initiation, though eGFR did recover from this and stabilize. After month 5, there was no significant difference in eGFR between dippers and non-dippers. At last follow up (8 mo post-SGLT2i initiation), eGFR in the dippers (67.9 ± 13.9, *n* = 24) was comparable to that of the non-dippers [67.9 ± 13.9 mL/min/1.73 m² (*n* = 24) *vs* 69.8 ± 19.0 mL/min/1.73 m² (*n* = 106), *P* = 0.358].

Though specific data on long term eGFR are lacking, Lim *et al*[13] did report a significant reduction in terms of SCr doubling in the SGLT2i cohort *vs* non-SGLT2i users in both unadjusted (HR = 0.49, 95%CI: 0.29-0.85) , adjusted (across multiple models: Adjusted HR (aHR) = 0.37-0.41, 95%CI: 0.22-0.90, all *P* < 0.05) , and propensity-score matching (aHR = 0.45, 95%CI: 0.23-0.88, *P* = 0.019) at 72 mo of follow up.

Proteinuria

Proteinuria was not assessed in these studies. As proteinuria is a major risk factor for and driver of progressive CKD, this is certainly an area that needs further studying.

Weight

Weight decreased in 8 studies with a median weight decrease of 1.95 kg (range: 0.7-3.2 kg)[8-10,12,14].

Blood pressure

Blood pressure changes were reported in 4 studies, with mixed results[8,9,11,12]. The magnitude of these changes was on the order of 7-9 mmHg, which are likely clinically significant. This is reaffirmed by findings in the ADVANCE trial, whereby Heerspink *et al*[15] showed that randomization to perindopril-indapamide compared to placebo in CKD ≥ 3 patients with diabetes for 5 years prevented 12 cardiovascular events with reductions in systolic blood pressure on the order of 4.5 mmHg.

Immunosuppression drug interactions

Though data on drug interactions with immunosuppression were limited, four studies did not observe clinically nor statistically significantly differences in drug trough levels after SGLT2i initiation[9-12].

Adverse events

Urinary tract infections (UTI) were the most common adverse event observed across the various studies. When reported, these ranged from none observed up to 36%. 4 studies reported rates between 13%-15%[8-10,14].

Genital infections (GI) occurred but less commonly than UTI in KTRs with only a few GI occurring in studies where it was distinctly described[9,14,16].

Graft function remained stable throughout these studies despite high angiotensin converting enzyme inhibitors (ACEi)/aldosterone receptor blockers (ARB) utilization and the observed eGFR dip at the 4-6 wk mark[10,12,13].

Leg amputation was not observed in any of the studies described. Schwaiger *et al*[16] reported on this in their study with empagliflozin. As is aptly described by Heyward *et al*[17] in their systematic review and meta-analysis, the risk for lower extremity amputation for SGLT2i use in the non-transplant population has only been observed with canagliflozin.

In these small studies, no episodes of euglycemic diabetic ketoacidosis were reported. Song *et al*[14] noted a wide range of insulin dose reductions post-SGLT2i incorporation. Hypoglycemia was noted infrequently in these studies (*n* = 2 per Lemke *et al*[10]). This risk for hypoglycemia is highest for those with well controlled diabetes (HgbA1c < 8) as well as those on insulin and/or sulfonylurea-class medications, as was the case in the Lemke *et al*'s study[10].

Cost

Lemke *et al*[10] identified cost as the highest reported reason for SGLT2i discontinuation (35%, *n* = 6). Over time, SGLT2i have become more affordable. Aggarwal *et al*[18] recently described out-of-pocket expenses for SGLT2i, noting that for

Table 1 Summary of studies on sodium-glucose cotransporter-2 inhibitor use in kidney transplant recipients

Ref.	Type, location	Follow up	Treatment arms	Inclusion/exclusion criteria	Baseline eGFR (mL/min/1.73 m²), HgbA1c (%)	Time from transplant	Result	Adverse events/treatment discontinuation	Comments
Lemke *et al*[10], 2022	Retrospective, United States	12 mo; 27 pts ≥ 12 mo	Cana (*n* = 12); Dapa (*n* = 3); Empa (*n* = 24)	T2DM or PTDM; SGLT2i; 4/2013 to 10/2020; care solely in health system	eGFR, median (IQR) 69 (54-76); HgbA1c Median (IQR) 8.4 (7.8-9.2)	Median (IQR) 28 mo (16-60)	HbA1c↓ (8.4-7.5 at 3 mo; 7.5 at 12 mo; eGFR ↔/Cr ↔ at 3/12 mo; Wt ↓1.6 kg	UTI (*n* = 6; 3 required hospital stay; 1 ICU). Diabetic foot ulcer (*n* = 2). Hypoglycemia (*n* = 2; insulin *n* = 1, glipizide *n* = 1). No DKA, AKI dehydration requiring IVF, Fournier gangrene, Genital infection, fractures. Discontinued tx: *n* = 17 [d/c after a median (IQR) 244d (117-401)], *n* = 6 for cost, *n* = 4, eGFR, *n* = 3 infection, *n* = 1 poor wound healing, *n* = 1, hypoglycemia, *n* = 1 self d/c, *n* = 1, death unrelated to SGLT2i	38% on ACEi/ARB at initiation. Insufficient proteinuria data; Tac levels stable. 5/6 had prior UTI, 4/6 continued SGLT2i w/o recurrence
Lim *et al* [13], 2022	Retrospective, South Korea	62 mo ± 42 mo	Empa (*n* = 150). Dapa (*n* = 76) *vs* non-SGLT2i (*n* = 1857)	T2DM or PTDM Pancreas Transplant Prescribed SGLT2i < 90 from transplant	eGFR at 3 mo post-transplant 66.9 ± 17.7 *vs* 68.4 ± 20.1. HgbA1c at 3 mo post-transplant. Both 7.3 ± 1.4	Mean 3.8 yr ± 4.5	A risk primary outcome = composite outcome of all-cause mortality, DCGF, and SCr doubling: Multivariate [aHR (0.43; 95%CI = 0.24-0.78, *P* = 0.006) propensity score-matched; aHR (0.45; 95%CI = 0.24-0.85, *P* = 0.013)]. HbA1c = NR. eGFR stable at 8 mo. ↓SCr doubling significantly in unadjusted and adjusted models. Wt = NR	UTI/genital mycotic infection: (SGLT2i 4.5 events/100 patient-year *vs* non-SGLT2i 6.2/100 patient-year). No DKA. Discontinued txt: NR	15.6% eGFR dip over 10% during first month. eGFR recovered thereafter. 48.7% of the SGLT2i cohort was on ACEi/ARB. Composite all-cause mortality, DCGF, or SCr doubling in KTRs
Hisadome *et al*[12], 2021	Retrospective observational study, Japan	48 wk	SGLT2i (*n* = 29); Cana (*n* = 9); Empa (*n* = 4); Dapa (*n* = 3); Luseo (*n* = 5); Ipra (*n* = 7); Tofo (*n* = 1) *vs* Other oral glycemic agent (*n* = 60); DDP4i (*n* = 42); meglitinides (*n* = 9); metformin (*n* = 4); SU (*n* = 4) α-glucosidase	ESRD patients w/T2DM nephropathy pre-transplant PO hypoglycemic. Follow up at outside centers < 1 yr follow up. Missing data	eGFR mean ± SD: 50.4 ± 13.9; 47.5 ± 13.1. HgbA1c mean ± SD: 7.7 ± 0.9; 7.6 ± 1.1	NR	HgbA1c 7.7 -> 7.6 (same) *vs* 7.6 to 7.5. Wt -0.7 ± 5.1 kg *vs* 1.6 ± 4.5 kg. eGFR 50.4 -> 51.4 *vs* 47.5 to 46.3. BP went up (7 mmHg ± 20 *vs* -3 ± 24)	UTI 2:0; CV disease 0:2. BPAR 1:1. Discontinued txt: NR	71.2% of the SGLT2i group was also on ACEi/ARB. Stable tac levels (*P* = 0.755)
Song *et al* [14], 2021	Retrospective, United States	101 d	Empa (*n* = 43); Cana (*n* =6); Dapa (*n* = 1)	PTDM eGFR ≥ 30. AKI in prior ≤ 30 d. UTI in prior 6 mo	eGFR at initiation: Mean 66.7; 30-45 (*n* = 7; 14%) HbA1c mean ± SD: 7.1 ± 0.1	Median (IQR): 319.5 d (122-696). 40% within 200 d	ΔeGFR 3 mo: -1 mL/min; 6 mo: 1 mL/min. ΔHgbA1c 0.53%. Treated UTI 7 (14%). Approx-imately 20% typical rate. Change in insulin (-3.7 units ± 22.8). Wt (-2.95 kg ± 3.54, 95%CI 3.53-1.5). HgbA1c ↔; eGFR ↔; Wt↓. ΔMag2+ ↑ by 0.13	UTI (*n* = 7). D/C txt: *n* = 9 (5, UTI; 1 genital infection, 1; native disease; recurrence, 1 PTDM; resolution, 1; physician preference)	80% T2DM; 98% on prednisone; UTI rate comparable to KT population (14%)

AlKindi *et al*[8], 2020	Retrospective case series, United Arab Emirates	Range: 3 mo to 2 yr	Empa 10 mg *n* = 5; 25 mg *n* = 1. Dapa 25 mg *n* = 2	Diabetic KTRs; SGLT2i between 06/16-01/19	eGFR mean ± SD: 75.8 ± 13.4; HbA1c mean ± SD: 9.3 ± 1.4	mean ± SD: 9.6 yr ± 6.41	HgbA1c↓ (9.0 at 3 mo; 8.6 at 6 mo; 7.7 at 9 mo; 7.4 at 12 mo; eGFR ↔ median eGFR 72 (range 62-76) at 12 mo. Wt (mean wt 84.82 kg -> 82.87 at 3 mo -> 82.75 at 6 mo). BP not statistically significant though 9 pt difference	UTI + hospitalization (*n* = 1); pt w hx of UTI no UTI w ppx. Discontinuation rate: NR	2/8 T2DM; 6/8 PTDM; all LURKTx
Halden *et al*[9], 2019	Prospective, double blind, RCT Norway	6 mo	Cana 10 mg (*n* = 22). Placebo (*n* = 22)	≥ 18 yr; ≥ 1 yr post-transplant. PTDM only < 20% SCr deviation in last 2 mo. ≥ 3 mo stable immunosuppression. eGFR ≤ 30; Pregnant or nursing	eGFR Median (IQR) 66(57-68): 59 (52-72). HbA1c Median (IQR) 6.9 (6.5-8.2): 6.8 (6.1-7.2)	Median (IQR) 3 yr (1-16): 3 yr (1-15)	HbA1c↓ (6.9 to 6.7 *vs* 6.6 to 6.9); eGFR↓ (2 mo), ↔ (6 mo)-66 to 61 *vs* 59 to 59. Weight↓ (92 kg to 88.8 kg *vs* 84 to 85 kg). No real impact on BP. Hgb increase 13.9 to 14.5. ↓Uric acid. Tac/CSA/Siro levels stable	Urosepsis 1:0 (hx of recurrent UTI), UTI 3:3, genital infection 1:0, hematuria 1:0. Discontinued txt: *n* = 2 (recurrent UTI, urosepsis): 3 (withdrew consent, colon cancer, no longer PTDM)	High DPP-4i use; most were not on additional therapy
Schwaiger *et al*[16], 2019	Prospective	1 mo (*n* = 14); 12 mo (*n* = 8)	Empagliflozin (*n* = 14). Reference (*n* = 24)	eGFR > 30; < 40 IU/d insulin. HgbA1c < 8.5. Adequately diagnosed PTDM	Baseline. eGFR 55.6. Baseline HgbA1c 6.5	Median 69.4 ± 57.2 mo	HgbA1c 6.5-> 6.6 at 4 wk (*P* > 0.05). eGFR 55.6 -> 47.5 at 4 wk (*P* > 0.05). Average TBW↓ 1.6 kg; Waist circ ↓4 cm. ECV/TBFV decreased	UTIs: 5:9. Genital infection: 1. AKI, DKA, Fournier's-NR	100% on steroids. Median onset of PTDM was 0.5 months. 100% on insulin
Shah *et al* [11], 2019	Prospective	6 mo	Canagliflozin (*n* = 25)	≥ 18 years old. CrCl (ml/min) > 60; HgbA1c > 6.5; T2DM; PTDM. Unstable Cr. ALT > 2 × ULN; TBili > 2 × ULN; Recent UTI/genital mycotic infection	Baseline Cr (mg/dL): 1.1 ± 0.2; Baseline HgbA1c: 8.5 ± 1.5	Mean duration of transplant = 2.7 yr (0.2-13.2)	HgbA1c: 8.5 ± 1.5 -> 7.6 ± 1. Cr: 1.1 ± 0.2 -> 1.1 ± 0.3. Weight: 78.6 ± 12.1 -> 76.1 ± 11.2 (*P* < 0.05). SBP (mmHg): 142 ± 21 -> 134 ± 17 (*P* < 0.05)	No increase in UTI/genital infections. No hypoglycemia or DKA. Fatigue (*n* = 3). Discontinued treatment (*n* = 1)	20 T2DM; 5 PTDM. Reduction of other hypoglycemics needed. 1 KTR self d/ced. Used fixed 100 mg dose. Stable tac doses

eGFR: Estimated glomerular filtration rate; pts: Patients; Cana: Canagliflozin; Dapa: Dapagliflozin; Empa: Empagliflozin; T2DM: Type 2 diabetes mellitus; PTDM: Post-transplant diabetes mellitus; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; IQR: Interquartile range; HgbA1c: Glycohemoglobin; Cr: Creatinine; Wt: Weight; UTI: Urinary tract infection; ICU: Intensive care unit; DKA: Diabetic ketoacidosis; AKI: Acute kidney injury; IVF: Intravenous fluids; txt: Treatment: d/c: Discontinued; ACEi: Angiotensin converting enzyme inhibitors; ARB: Aldosterone receptor blockers; tac: Tacrolimus; SCr: Serum creatinine; DCGF: Death censored graft failure; aHR: Adjusted hazard ratio; CI: Confidence interval; NR: Not reported; KTR: Kidney transplant recipient; Luseo: Luseogliflozin; Ipra: Ipragliflozin; Tofo: Tofogliflozin; DDP4i: Dipeptidyl peptidase 4 inhibitors; ESRD: End stage renal disease; PO: Oral; SD: Standard deviation; BP: Blood pressure; CV: Cardiovascular; BPAR: Biopsy proven acute rejection; Δ: Change in; Mag2+: Magnesium; KT: Kidney transplant; hx: History; ppx: Prophylaxis: LURKTx: Living unrelated kidney transplant; Hgb: Hemoglobin; CSA: Cyclosporine; siro: Sirolimus; IU: International units; TBW: Total body weight; circ: Circumference; ECV: Extracellular volume; TBFV: Total body fluid volume; CrCl: Creatinine clearance; ALT: Alanine transaminase; ULN: Upper limit of normal; TBili: Total bilirubin; SBP: Systolic blood pressure.

most insured patients, median cost for 30 d of SGLT2i therapy cost around $38.43 (range: $3.87-$49.42)[18].

Novel findings
In their comprehensive randomized controlled trial, Halden *et al*[9] observed increased hemoglobin/hematocrit and decreased uric acid levels with SGLT2i use. Song *et al*[14] observed an improvement in serum magnesium levels after SGLT2i initiation.

Long term outcomes
Lim *et al*[13] showed a significant reduction at five years in their composite outcome of all-cause mortality, death-

censored graft failure (DCGF), and serum creatinine doubling with SGLT2i use in both multivariate (aHR = 0.43; 95%CI: 0.24-0.78, *P* = 0.006] and propensity score-matched aHR (0.45; 95%CI: 0.24-0.85, *P* = 0.013). Otherwise, these studies lacked long term outcome data.

ANALYSIS

Though these studies are heterogenous and limited in terms of design and size, short term safety and efficacy outcomes of SGLT2i use in diabetic KTRs appear comparable to those observed in CKD patients with diabetes.

Glycemic control paralleled that seen in the non-transplant DM population with modest HgbA1c improvements. Though most studies included KTRs with adequate allograft function, Hisadome *et al*[12] and Song *et al*[14] included a substantial number of individuals with eGFR in the 30-45 range, which approximates to CKD stage 3b. Though there are potential differences between CKD and CKD after transplant as described by Djamali *et al*[19], evidence supporting safe, effective use of SGLT2i in KTRs with decreased allograft function is encouraging.

Remarkably, the eGFR decline, recovery and stabilization of kidney function that occurs in non-transplant diabetics was also observed in some KTRs without significant unfavorable impacts on long term graft function. This was in the setting of high reported concurrent ACEi/ARB use which are recommended as first line agents in diabetic kidney disease. This is exciting, as renin-angiotensin-aldosterone system (RAAS) blockade plays a vital role in diabetic CKD/cardiovascular management. Moreover, the major trials for SGLT2i, such as EMPA-REG OUTCOME by Wanner *et al*[20] reported RAAS blockade use between 80%-85% of those studied. In summary, the illustration of eGFR stability with simultaneous use of SGLT2i/RAAS blockade in KTRs across multiple studies will hopefully quell clinician fears regarding their concurrent use.

It is unfortunate that proteinuria was not an endpoint in any of the included studies. Results of studies in the general population, namely those by Jongs *et al*[21], Cherney *et al*[22], and Trujillo *et al*[23], in terms of SGLT2i effect on proteinuria, are both limited and mixed[21-23]. EMPA-REG OUTCOME by Wanner *et al*[20], CANVAS by Neal *et al*[24] and CREDENCE by Perkovic *et al*[25] and DAPA-CKD by Heerspink *et al*[5], suggested utility for these agents in reducing the geometric mean urinary albumin creatinine ratio, increasing the likelihood of regression in albuminuria stage and reducing the risk of macroalbuminuria progression[20,21]. Further investigations into whether or not SGLT2i impact proteinuria in KTRs will be important not only to better understand these medications, but also to help with agent selection if a difference *e.g.*, empagliflozin and canagliflozin *vs* DAPA, is observed between them in KTRs.

Weight loss occurred in almost every study, likely due to the osmotic diuresis caused by SGLT2i use. This is also occurring due to fat loss from caloric wasting *via* glucose. As the weight loss demonstrated for most patients is less than 5% total body weight, this likely has little bearing clinically.

That being said, perhaps weight loss can underscore future studies examining impacts on truncal obesity, waist size (as Schwaiger *et al*[16] remarked), cholesterol, uric acid levels, and other markers of obesity/metabolic syndrome and their impacts on kidney and cardiovascular outcomes.

Blood pressure outcomes were less clear across these studies, which is at least partly explained by the different mechanisms and influences on blood pressure in KTRs compared to CKD patients as described by Kasiske *et al*[26]. It is unlikely due to weight loss alone given the magnitude of weight loss as previously noted. As these medications are studied further in KTRs, perhaps novel mechanisms for how SGLT2i influence blood pressure will be elucidated.

While UTIs were observed in these studies, they did not appear to occur significantly more than in KTRs not on SGTL2i. As described by Brune *et al*[27], the prevalence of UTI after transplant varies significantly based on several factors (namely *via* definition, study, population, length of follow up). However, they state that a reasonable benchmark based on larger studies is a 1-year incidence rate around 30%. Lemke *et al*[10] reported continued use of SGLT2i after UTI, with one of those patients requiring hospitalization for treatment, but without recurrent disease. Long term impacts of SGLT2i use/glucosuria not only on UTI risk, but also asymptomatic bacteriuria, antibiotic use and associated complications are ongoing uncertainties. GI were observed but at a fairly low rate compared to UTI as described above.

Though limited, drug level data suggest that SGLT2i have little to no impact on calcineurin inhibitor (CNI) trough levels, nor were increased episodes of rejection observed. As Scheen[28] describes in his excellent review on the subject, SGLT2i metabolism minimally involves cytochrome CYP3A4, making SGLT2i-CNI drug interactions slight at best.

As described by Song *et al*[14], hypomagnesemia was improved in KTRs on SGLT2i. As hypomagnesemia is associated with increased risk of cardiovascular and infection-related mortality as noted by Panthofer *et al*[29] and Odler *et al*[30] and this is an important management target. Per Huang *et al*[31], there may be a role for pre-emptive SGLT2i use as hypomagnesemia itself has been shown to increase the risk of PTDM in KTRs. Additionally, hypomagnesemia treatment can be challenging as most magnesium formulations cause diarrhea. Therefore, SGLT2i may play a role obviate/minimize high magnesium supplementation needs.

Though not discussed thoroughly in the literature, Bilezikian *et al*[32] and Kohan *et al*[33] note that there are some concerns for SGLT2i and their impacts on bone health. Lemke *et al*[10] reported on fractures in their study, noting none occurred. Though this is a nascent area of research, Blau and Taylor[34] demonstrated a possible mechanism *via* the FGF23–1,25-dihydroxyvitamin D–parathyroid hormone axis. As impaired bone health is common in KTRs, seeing how this relationship bears out in longer, more robust studies will be important for patient selection and ongoing management. At the moment, there is insufficient data to attribute substantial fracture risk to SGLT2i use.

With SGLT2i being relatively new agents, there is a paucity of data on long-term kidney, cardiovascular, and survival outcomes. Determination of their impact on long-term outcomes will require larger, protracted investigations. This is illustrated in the EMPA-REG trial by Wanner *et al*[35], in which SGLT2i-mediated eGFR preservation was first seen

around 80 wk of therapy *vs* placebo.

Ideally, future retrospective studies, like that by Lim *et al*[13] and/or prospective analyses can describe these relationships going forward. These would be best achieved by multi-center, large trials analogous to their landmark predecessors.

In their comprehensive study review on the management of PTDM, Hecking *et al*[36] aptly summarize direct and indirect potential benefits of SGLT2i in kidney transplantation. Though some of this is extrapolated from non-KT research, novel impacts such as reduction in vascular rigidity as well as hypoxia-inducible factor-1, could be impactful in the kidney transplant population regarding cardio-/reno-/vascular health, anti-inflammatory properties and perhaps anemia management as described by Hecking *et al*[36], Gupta and Wish[37].

A key limitation of these studies is that they evaluated KTRs with diabetes alone. As this is a logical starting place for investigating the efficacy of SGLT2i, to suggest that these medications are limited only to KTRs with diabetes is too narrow a view. With kidney transplantation existing as a state of CKD as well as ESKD itself portending significant cardiovascular risk, we surmise (and hope) that the benefits of SGLT2i will extend to KTRs without diabetes as well. As was demonstrated in DAPA-CKD, a multicenter randomized controlled trial of 4304 patients in which 32.5% of the patients were non-diabetic, SGLT2i increased the likelihood of albuminuria regression and reduced the likelihood of progression to more severe stages of albuminuria in CKD patients with and without diabetes[5]. Therefore, KTRs without diabetes warrant investigation into the utility of SGLT2i use.

CLINICAL RECOMMENDATIONS

Though more research is needed, there appears to be a subset of non-insulin dependent diabetic KTRs who ought to benefit from SGLT2i therapy.

Identifying appropriate candidates is a critical step for implementing SGLT2i therapy routinely. Though questions remain presently regarding long term safety, the stalwart evidence from the CKD literature is compelling for the transplant community to press forward.

In their recent review, Patel *et al*[38] proposed an "ideal" KTR SGLT2i candidate. While this provides a nice general framework, we have additional characteristics to build on this model for identifying SGLT2i candidates.

At present, there does not appear to be substantial evidence on when post-transplant to initiate SGLT2i therapy. Earlier initiation *i.e.*, prior to 6- or 12-mo post-transplant may be beneficial for at least 3 reasons: (1) PTDM appears to be an early post-transplant complication. This is shown by Jenssen and Hartmann[39], in their review on PTDM, where they cite Porrini *et al*[40]. In their study, 32% of the cohort developed PTDM (215/672). Of these 215, 187 (87%) of these KTRs developed PTDM prior to 12 mo; (2) major benefits of SGLT2i therapy such as eGFR preservation may require long term medication use, as EMPA-REG showed[35]; and (3) as is aptly described by Wolfe *et al*[41] in their seminal study on mortality after deceased donor kidney transplant (DDKT), there is increased risk of death in the early post-transplant time period. Perhaps this will promote studies of initiating SGLT2i at the time of transplantation in select patients *e.g.*, DDKT with immediate graft function.
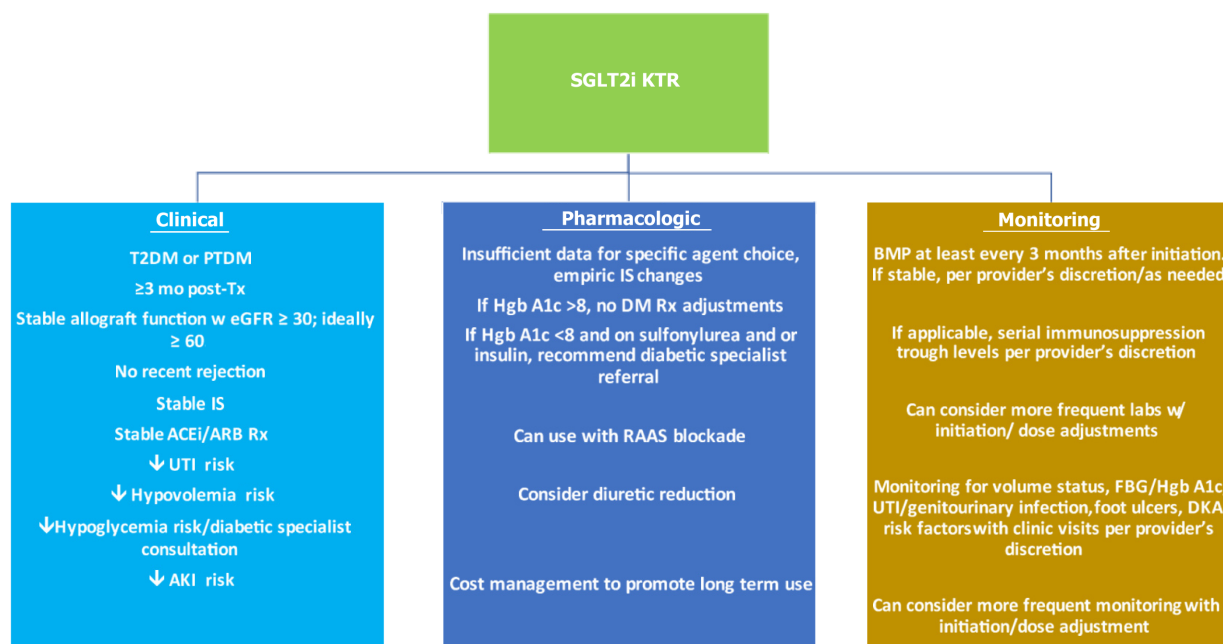
In the following section, we will put forth clinical recommendations for SGLT2i use in KTRs. These are based on the aforementioned results as well as inclusion/exclusion criteria in the studies reviewed. As this is an evolving science, these are solely recommendations *i.e.*, provider discretion remains crucial to using these medications. These are also summarized in Figure 1.

Based on the literature reviewed, we propose the following as good candidates for SGLT2i use: (1) KTRs with pre-transplant T2DM or PTDM; (2) at least 3 mo post-transplant; (3) stable allograft function preferably with eGFR of at ≥ 30 mL/min/1.73 m^2, ideally ≥ 60 mL/min/1.73 m^2 for the past 2 mo; (4) no rejection episodes within the past 3 mo; (5) at least 3 mo of stable immunosuppression; (6) stable ACEi/ARB doses; (7) patients at low risk for volume depletion *e.g.*, low risk for unstable diarrhea, vomiting; (8) patients at low risk for hypoglycemia *e.g.*, HgbA1c > 8 or < 8 and not on a sulfonylurea or insulin. If at risk for hypoglycemia, would consult diabetic specialist for regimen titration; (9) patients without significant UTI history or diabetic foot ulcers; (10) patients with low risk for acute kidney injury; and (11) patients who may benefit from novel aspects of SGLT2i: Hypomagnesemia, hyperuricemia, anemia.

In terms of pharmacologic therapy titration in the context of SGLT2i initiation, we recommend the following: (1) Insufficient data to support empiric adjustments to maintenance immunosuppression or to diabetic prescriptions; (2) can consider reducing diuretic doses; (3) advise diabetic specialist consultation for KTRs with well controlled diabetes (HgbA1c < 8) and other diabetic agents, particularly insulin or sulfonylureas, to help titrate their diabetic regimen to minimize the risk of hypo-glycemia; and (4) continued drug trough and blood glucose monitoring are key to titrate further.

In terms of monitoring parameters, we recommend the following: (1) Renal function assessment at least every 3 mo at a minimum. Can consider more frequent monitoring with initiation/dose adjustments; (2) if applicable (on CNI or mammalian target of rapamycin inhibitor therapy), serial immunosuppression trough levels per provider's discretion. Can consider more frequent monitoring with initiation/dose adjustments; (3) routine monitoring for volume status, risk factors for diabetic ketoacidosis, hypoglycemia; and (4) routine monitoring for signs and symptoms of UTI, diabetic foot ulcers.

It is somewhat challenging to put forth contraindications to use at this time, particularly when the evidence for use is so persuasive. Assuredly there are patients in whom SGLT2i use poses greater risk of harm than benefit *e.g.*, a KTR with a history of DKA, at risk for or experiencing recurrent transplant pyelonephritis, and/or chronic osteomyelitis and/or active diabetic foot wounds. Ultimately, the determination of benefit *vs* risk requires clinical reasoning, evaluation and

SGLT2i KTR

Clinical

T2DM or PTDM

≥3 mo post-Tx

Stable allograft function w eGFR ≥ 30; ideally ≥ 60

No recent rejection

Stable IS

Stable ACEi/ARB Rx

↓ UTI risk

↓ Hypovolemia risk

↓Hypoglycemia risk/diabetic specialist consultation

↓ AKI risk

Pharmacologic

Insufficient data for specific agent choice, empiric IS changes

If Hgb A1c >8, no DM Rx adjustments

If Hgb A1c <8 and on sulfonylurea and or insulin, recommend diabetic specialist referral

Can use with RAAS blockade

Consider diuretic reduction

Cost management to promote long term use

Monitoring

BMP at least every 3 months after initiation. If stable, per provider's discretion/as needed

If applicable, serial immunosuppression trough levels per provider's discretion

Can consider more frequent labs w/ initiation/ dose adjustments

Monitoring for volume status, FBG/Hgb A1c, UTI/genitourinary infection, foot ulcers, DKA risk factors with clinic visits per provider's discretion

Can consider more frequent monitoring with initiation/dose adjustment

Figure 1 Clinical, pharmacologic and monitoring parameters for sodium glucose cotransporter-2 inhibitor use in a kidney transplant recipient. Clinical criteria, pharmacologic and monitoring strategies are essential to selecting and managing kidney transplant recipient (KTRs) for sodium-glucose cotransporter-2 inhibitor (SGLT2i) use. Stable KTRs with an appropriate diabetes diagnosis, clinical stability and low risk for adverse events is key. Little data exists for empiric medication changes, though diuretic dose reduction ought to be considered. Strategies for cost management beyond insurance ought to be explored to maximize possible long-term benefit from SGLT2i administration. Laboratory and clinical monitoring more frequently with initiation/dose adjustments is critical to identifying adverse events. SGLT2i: Sodium-glucose cotransporter-2 inhibitors; KTR: Kidney transplant recipient; T2DM: Type 2 diabetes mellitus; PTDM: Post-transplant diabetes mellitus; Tx: Transplant; w: With; eGFR: Estimated glomerular filtration rate; IS: Immunosuppression; ACEi: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; Rx: Prescription; UTI: Urinary tract infection; AKI: Acute kidney injury; Hgb: Hemoglobin; DM: Diabetes mellitus; RAAS: Renin-angiotensin-aldosterone system; FBG: Fasting blood glucose; DKA: Diabetic ketoacidosis.

patient-provider dialogue on whether SGLT2i use is in the patient's best interest.

Notably, guidance exists in the literature regarding patient handout communications when initiating SGLT2i therapy. Lam *et al*[42] provide an excellent version that is generally applicable to KTRs.

LIMITATIONS

Though early data on SGLT2i implementation in KTRs is promising, it is albeit limited.

There are 3 main limitations in the data on the use of SGLT2i in KTRs. Longitudinal studies with large enrollment volume are absent. The longest follow up was around 8.5 years with most having far less. This leaves cardiovascular, graft and mortality outcomes unexplored. Rare adverse events like euglycemic DKA or osteoporosis are also not explored. RCTs are necessary to establish causality and bolster clinical practice recommendations. Most of the studies in SGLT2i are limited to retrospective, observational design or case series.

The SGLT2i story is one that is well underway. There appears to be substantial evidence supporting their use in terms of safety and short-term efficacy based on the studies we described and their antecedents. What lies ahead regarding long-term SGLT2i therapy is unknown. With SGLT2i, we are not working *ab initio* (from the beginning). Rather, as is precedent in some of the greatest epics and sagas (*i.e.*, the *Mahābhārata,* Homer's *Iliad* and *Odyssey*, Virgil's *Aeneid,* Dante's *Divine Comedy*) as noted by Lochtefeld[43], Murray[44] and Raffa[45], we can and ought to forge ahead into the unknown *in medias res*-into the middle of things.

FUTURE DIRECTIONS

While the current literature gives insight into short-term outcomes of SGLT2i use in KTRs, more research is needed to identify the long-term impacts of SGLT2i use in this population.

Currently, there are 2 actively recruiting clinical trials (NCT04965935 aka INFINITI2019 and NCT04906213 aka CREST-KT).

INFINITI2019 is a double-blind, placebo-controlled trial aimed at comparing DAPA to placebo in 52 KTRs. The primary outcome is blood pressure reduction in addition to fasting blood glucose, HgbA1c, continuous home glucose

monitoring, arterial stiffness, systemic vascular resistance, change in baseline measured GFR, change in eGFR, proximal tubular natriuresis, albuminuria, change in baseline urinary and plasma oxidative stress markers, change in tubule interstitial hypoxia, CNI levels, and adverse events.

CREST-KT is a single-center, double-blinded randomized controlled trial of empagliflozin therapy in 72 KTRS with (36) and without (36) diabetes. After dividing by diabetes diagnosis, the groups will be randomized 2:1 to empagliflozin 10 mg *vs* placebo *i.e.*, 48 KTRs will be on empagliflozin and 24 KTRS will be on placebo. Study time is planned to be 18 mo.

Primary outcomes include: Change in eGFR, change in albuminuria, change in cardiac structure by 3D echocardiogram, change in blood insulin level, change in fasting blood sugar, # of UTIs and # of GI.

Secondary outcomes include: Change in kidney biopsy from time zero to 6 mo and change in HgbA1c as well as AEs.

In addition to these studies, hopefully future randomized controlled trials examining long term renal outcomes as well as cardiovascular outcomes, particularly in patients with known heart failure, will help guide appropriate SGLT2i use and influence guidelines and practice patterns for SGLT2i in KTRs.

CONCLUSION

SGLT2i appear to be safe, effective medications in the arsenal of post-transplant therapies for select KTRs. Our present literature, though somewhat limited, is founded on preceding strong research in CKD patients with diabetes. Concurrent research and utilization of SGLT2i is vital to not only identify long-term patient, graft and cardiovascular outcomes of these agents, but also to augment diabetic, CKD, and cardiovascular management in KTRs *in media res*.

FOOTNOTES

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