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Sodium-Glucose Cotransporter-2 Inhibitor Use in Kidney Transplant Recipients

SGLT2i use in KTRs

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Abstract

BACKGROUND

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) or "gliflozins", are novel oral hypoglycemic agents that have garnered much attention in the worlds of nephrology and cardiology for their substantial benefits. These recent data have positioned SGLT2i at the forefront of diabetic chronic kidney disease and heart failure management. SGLT-2i use post-kidney transplant is an emerging area of research.

AIM

In this mini review, we aim to summarize current literature describing SGLT2i in kidney transplant recipients to 1. provide a comprehensive resource and clinical decision-making aid and 2. cultivate future research.

METHODS

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, kidney transplant recipients, type 2 diabetes mellitus, post-transplant diabetes mellitus.”

We limited our search to studies with available full text and English language.

RESULTS

In this sample, empagliflozin (n = 241) was the most prescribed SGLT2i followed by dapagliflozin (n = 85) and canagliflozin (n = 74). 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/1.73m^2 (range 50.4-75.8). Median Hgb A1c at initiation was 7.7% (range 6.9-9.3).

SGLT2i were demonstrated to be effective as demonstrated by favorable short-term outcomes including Hgb A1c, eGFR, as well as novel impacts on hemoglobin/hematocrit, uric acid, and magnesium levels. They were demonstrated to

be safe in KTRs with low adverse event rates of infections, hypoglycemia, euglycemic diabetic ketoacidosis, and stable tacrolimus levels. More data is needed to demonstrate long term outcomes.

CONCLUSION

SGLT2i appear to be safe, effective medications in the arsenal of post-transplant therapies for select kidney transplant recipients. 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, chronic kidney disease, and cardiovascular management in kidney transplant recipients

Key Words: Sodium glucose cotransporter-2; Sodium glucose cotransporter-2 inhibitor; kidney transplantation; diabetes; post-transplant diabetes mellitus; new onset diabetes after transplant.

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Core Tip: Multiple large trials have demonstrated sodium-glucose cotransporter-2 inhibitor (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. 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. [1] SGLT2i reduces the glucose excretion threshold to 2.2mmol/L (40 mg/dL) from 10mmol/L (180 mg/dL).[2,3] Consequently, they have been shown to reduce Hgb A1c 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 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% (HR = 0.55, 95%CI: 0.48-0.64, p <0.0001), and cardiovascular death or heart failure hospitalization 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. DAPA-CKD showed that dapagliflozin in CKD patients with or without diabetes reduced the risk of a composite outcome of 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 to 27). [5]

As shown by adoption of SGLT2i as first line therapies for CKD patients with diabetes by the 2022 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, evidence

for these agents is promising. [6] 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. 40% of waitlisted patients have DM and 15-30% of non-diabetic patients develop post-transplant diabetes mellitus (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 AKI/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.

MATERIALS AND METHODS

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, kidney transplant recipients, 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 diabetes mellitus (T2DM) and/or post-transplant diabetes (PTDM) in kidney transplant recipients (KTR)s 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: Hgb A1c, 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.

RESULTS

In this sample, empagliflozin (*n* = 241) was the most prescribed SGLT2i followed by dapagliflozin (*n* = 85) and canagliflozin (*n* = 74). 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/1.73m^2 (range 50.4-75.8). Median Hgb A1c at initiation was 7.7% (range 6.9-9.3).

The following results were seen and are summarized in Table 1.

Hgb A1c

Hgb A1c 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 A1c of 9.3 at initiation as well as excellent allograft function, Hgb A1c 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 Hgb A1c 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 SGLT2 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/1.73m^2 ,[n = 24] *vs* 69.8 ± 19.0 mL/min/1.73m^2 [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: 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 ACEi/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 (Hgb A1c <8) as well as those on insulin and/or sulfonylurea-class medications, as was the case in the Lemke 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 most insured patients, median cost for 30 days 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 (adjusted hazard ratio [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.

DISCUSSION

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 Hgb A1c 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 is CKD stage 3B. Though there are potential differences between CKD and chronic kidney disease after transplant (CKD-T), as has been described in the literature, several studies emphasize that SGLT2i can be effective below an eGFR of 45 mL/min/1.73m^2. [19]

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 RAAS blockade plays a vital role in diabetic CKD/cardiovascular management. Moreover, the major trials for SGLT2 inhibitors, such as EMPA-REG OUTCOME, reported RAAS blockade use between 80-85% of those studied. [20] 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. As Results of studies in the general population in terms of SGLT2i effect on proteinuria are both limited and mixed. [21-23] EMPA-REG outcome, CANVAS, and CREDENCE and DAPA-CKD 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.[20,21,24,25] 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* dapagliflozin, 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.[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.

Genital infections 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 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, this is an important management target. [29,30] There may be a role for pre-emptive SGLT2i use as hypomagnesemia itself has been shown to increase the risk of PTDM in KTRs. [31] 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, there are some concerns for SGLT2i and their impacts on bone health.[32,33] 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, in which SGLT2i-mediated eGFR preservation was first seen around 80 wk of therapy *vs* placebo. [35]

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 (HIF)-

1, could be impactful in the kidney transplant population regarding cardio-/reno-/vascular health, anti-inflammatory properties and perhaps anemia management. [36,37]

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. Therefore, kidney transplant recipients 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-months 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 *et al*[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] 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 kidney transplant recipients. 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:

-KTRs with pre-transplant T2DM or PTDM

-At least 3 mo post-transplant

-Stable allograft function preferably with eGFR of at ≥30 mL/min/1.73m^2, ideally ≥ 60 mL/min/1.73m^2 for the past 2 mo

-No rejection episodes within the past 3 mo

-At least 3 mo of stable immunosuppression.

-Stable ACEi/ARB doses

-Patients at low risk for volume depletion *e.g.*, low risk for unstable diarrhea, vomiting.

-Patients at low risk for hypoglycemia *e.g.*, Hgb A1c >8 or <8 and not on a sulfonylurea or insulin. If at risk for hypoglycemia, would consult diabetic specialist for regimen titration.

-Patients without significant UTI history or diabetic foot ulcers

-Patients with low risk for acute kidney injury

-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:

-Insufficient data to support empiric adjustments to maintenance immunosuppression or to diabetic prescriptions.

-Can consider reducing diuretic doses

-Advise diabetic specialist consultation for KTRs with well controlled diabetes (Hgb A1c <8) and other diabetic agents, particularly insulin or sulfonylureas, to help titrate their diabetic regimen to minimize the risk of hypoglycemia.

-Continued drug trough and blood glucose monitoring are key to titrate further.

In terms of monitoring parameters, we recommend the following:

-Renal function assessment at least every 3 mo at a minimum. Can consider more frequent monitoring with initiation/dose adjustments.

-If applicable (on CNI or mTOR therapy), serial immunosuppression trough levels per provider's discretion. Can consider more frequent monitoring with initiation/dose adjustments.

-Routine monitoring for volume status, risk factors for diabetic ketoacidosis, hypoglycemia

-Routine monitoring for signs and symptoms of urinary tract infections, 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 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 SGLT2 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 use of SGLT2i in KTRs. Lengthy 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 bolsters clinical practice recommendations. Most of the studies in SGLT2i are limited to retrospective, observational 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)*, we can and ought to forge ahead into the unknown *in medias res* – into the middle of things.[43-45]

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 dapagliflozin to placebo in 52 KTRs. The primary outcome is blood pressure reduction

in addition to fasting blood glucose, Hgb A1c, 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 10mg *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 genital infections.

Secondary outcomes include: Change in kidney biopsy from time zero to 6 mo and change in Hgb A1c 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 SGLT2 inhibitor use and influence guidelines and practice patterns for SGLT2i in kidney transplant recipients.

CONCLUSION

SGLT2i appear to be safe, effective medications in the arsenal of post-transplant therapies for select kidney transplant recipients. 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, chronic kidney disease, and cardiovascular management in kidney transplant recipients *in media res*.

ARTICLE HIGHLIGHTS

Research background

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are practice changing pharmaceutical agents that have changed the landscape of clinical care for patients living with kidney and heart disease. This has been illustrated in landmark randomized control trials that are some of the most robust studies in the field to date. With kidney transplant patients living with diabetes having chronic kidney disease (CKD) and significant cardiovascular comorbidities, study of how this class of medications impacts the kidney transplant population is paramount.

Research motivation

With cardiovascular disease and progressive chronic kidney disease and graft failure as major causes of morbidity and mortality to kidney transplant recipients, novel agents to mitigate these are of critical importance. Research into the efficacy, safety and long term outcomes of sodium-glucose cotransporter-2 inhibitors is vitally important to providing better care and improving outcomes for kidney transplant recipients. With nascent research in the field, we aimed to abridge this and provide clinical recommendations for application in clinical care.

Research objectives

The objective of this study was to compile recent studies of SGLT2i use in kidney transplant recipients in hopes of better understanding their efficacy, safety in this population as well as using them to derive clinical practice guidelines to aid clinicians in their prescribing and management practices in diabetic kidney transplant patients.

Research methods

We reviewed recent studies of SGTL2i use in kidney transplant recipients with type 2 diabetes or post-transplant diabetes mellitus limiting these to randomized control trials,

prospective case series or retrospective case series with comparison groups within the last 4 years.

Research results

Our review demonstrated that generally speaking SGLT2i have positive short term impacts on hemoglobin A1c, eGFR, and weight, albeit small. Their impacts on blood pressure vary from study to study and how they effect proteinuria in this population has yet to be studied in great detail. Moreover, novel benefits were observed in some studies such as their positive effect on anemia and hypomagnesemia. They appeared safe with low adverse event rates, including urinary and genital infections as well as meaningful impacts on immunosuppression levels. More data are needed to determine their impact on long-term outcomes of allograft, patient survival and cardiovascular outcomes.

Research conclusions

SGLT2i appear to be effective and safe medications for kidney transplant recipients in the short-term. Continued research, particularly with longer follow up, will be important to better identify their effect on long term outcomes.

Research perspectives

Future research includes randomized controlled trials with SGLT2i in diabetic kidney transplant recipients. Furthermore, trials are in line for non-diabetic KTRs based on the evidence in the general CKD population whereby SGLT2i were found to be effective in non-diabetic CKD.

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