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REVIEW

Recent advances in new-onset diabetes mellitus after kidney transplantation

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Abstract

A common challenge in managing kidney transplant recipients (KTR) is post-transplant diabetes mellitus (PTDM) or diabetes mellitus (DM) newly diagnosed after transplantation, in addition to known pre-existing DM. PTDM is an important risk factor for post-transplant cardiovascular (CV) disease, which adversely affects patient survival and quality of life. CV disease in KTR may manifest as ischemic heart disease, heart failure, and/or left ventricular hypertrophy. Available therapies for PTDM include most agents currently used to treat type 2 diabetes. More recently, the use of sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and dipeptidyl peptidase 4 inhibitors (DPP4i) has cautiously extended to KTR with PTDM, even though KTR are typically excluded from large general population clinical trials. Initial evidence from observational studies seems to indicate that SGLT2i, GLP-1 RA, and DPP4i may be safe and effective for glycemic control in KTR, but their benefit in reducing CV events in this otherwise high-risk population remains unproven. These newer drugs must still be used with care due to the increased propensity of KTR for intravascular volume depletion and acute kidney injury due to diarrhea and their single-kidney status, pre-existing burden of peripheral vascular disease, urinary tract infections due to immunosuppression and a surgically altered urinary tract, erythrocytosis from calcineurin inhibitors, and reduced kidney function from acute or chronic rejection.

Key Words: Cardiovascular disease; Glucagon-like peptide-1 receptor agonists; Kidney transplantation; Oral antihyperglycemic drugs; Post-transplant diabetes mellitus; Sodium glucose co-transporter 2 inhibitors; Dipeptidyl peptidase-4 inhibitors

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Core Tip: Kidney transplant recipients commonly develop post-transplant diabetes mellitus. Sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase 4 inhibitors are now available for treating type 2 diabetes mellitus. There is increasing evidence that these classes of drugs are effective in kidney transplant recipients, but caution is still advised due to their increased propensity otherwise for intravascular volume depletion, infections, and reduced kidney function.

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INTRODUCTION

Kidney transplantation (KT) is the renal replacement therapy of choice in patients with end-stage kidney disease (ESKD), improving quality of life and reducing mortality risk compared to dialysis[1]. However, an adverse effect of KT is post-transplant diabetes mellitus (PTDM). PTDM adversely affects patient survival and quality of life[2,3], leading to greater risk of graft loss, rejection, and infection, as well as diabetes-associated microvascular and macrovascular complications[4]. Graft failure for example is 50% higher in kidney transplant recipients (KTR) with diabetes than without diabetes, and recurrent diabetic kidney disease occurs in almost half of kidney allografts[5,6]. About one-third of nondiabetic KTR develop persistently impaired glucose metabolism by 6 mo post-transplantation[7-9]. Risk factors for PTDM include older recipient age, deceased donor graft, the use of calcineurin inhibitors (CNI) and corticosteroids, and adult polycystic kidney disease, in addition to traditional risks factors for type 2 diabetes (T2DM).

PTDM describes newly diagnosed T2DM after organ transplantation, regardless of timing or undetected pre-transplant presence, and is applied to clinically stable patients with persistent post-transplantation hyperglycemia[10]. Therefore, PTDM is often formally diagnosed at least 45 d post-transplant due to the high prevalence of early post-transplant hyperglycemia. The term PTDM now excludes known pre-existing diabetes mellitus (DM). Common measures to combat PTDM include early treatment with insulin, lifestyle interventions such as diet and exercise, bariatric surgery, and modified immunosuppression such as CNI and steroid avoidance. Since treatment approaches to pre-existing T2DM and PTDM do not significantly differ, the discussion of PTDM is taken throughout this review to encompass pre-existing DM.

Comprehensive reviews of PTDM have been published[11]. More recently, sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and dipeptidyl peptidase 4 inhibitors (DPP4i) are becoming increasingly available for managing T2DM. This update reviews the role of these newer agents in managing PTDM.

Current management of PTDM

At the 2013 international consensus meeting on PTDM, committee members were unable to endorse a hierarchical approach to using antihyperglycemic agents for managing PTDM. Suggestions included altering the immunosuppressive regimen and starting antihyperglycemic agents on an individualized basis[10]. CNI and steroid doses are often reduced, dietary counseling provided, and oral agents started. Despite the plethora of pharmacotherapy options for treating T2DM and by extension PTDM, there is paucity of evidence on the efficacy and safety of SGLT2i, GLP-1 RA, and DPP4i in KTR. In addition to healthy behavior interventions, metformin remains first line therapy in T2DM-associated chronic kidney disease (CKD) as well as PTDM[12-14]. Most recently, the Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines recommend metformin plus SGLT2i as first-line, followed by any other antihyperglycemic agent with GLP-1 RA being preferred as second line[15]. However, the safety and efficacy of SGLT2i when estimated glomerular filtration rate (eGFR) is < 30 mL/min per 1.73 m^2 in KTR is limited, but further studies will clarify their kidney and cardiovascular (CV) benefits[15].

Connecting PTDM to the cardiorenal syndrome

Managing PTDM connects to managing other facets of the cardiorenal syndrome, and as will be discussed in subsequent sections, can involve using SGLT2i, GLP-1 RA, and DPP4i. CV disease (CVD) leads causes of death in KTR, accounting for 30% of all deaths with a functioning graft[16,17]. KTR also carry a burden of other CV risk factors including hypertension, dyslipidemia, and obesity, all exacerbated by immunosuppressive medications[18]. KTR risk higher mortality than their age-matched counterparts without kidney disease[19]. This mortality risk is almost two-fold greater in PTDM[20]. For KTR with pre-existing diabetes, the risk of CVD and stroke increases threefold compared to non-diabetic recipients[21].

The most common CVD in KTR is ischemic heart disease (IHD), congestive heart failure (CHF) and left ventricular hypertrophy (LVH). IHD contributes over 50% to mortality in KTR[21]. CHF occurs 2-5 times more in KTR than the general population[22], reaching almost 20% by 3 years post-KT[23]. DM can cause heart failure (HF) independently of IHD *via* a diabetic cardiomyopathy with either preserved or reduced ejection fraction (HFpEF, HFrEF). HF is 2- to 4-fold more prevalent in DM and occurs earlier[24]. Diabetic nephropathy influences drug dosing in HF, resulting in treatment adjustments and failure to attain therapeutic targets. Risk factors for new-onset HF post-KT include DM[22,23,25]. LVH, a risk factor for sudden cardiac death in KTR, occurs in 50%-70% of this population. In non-KTR with T2DM, large CV and renal outcome trials of SGLT2i and GLP-1 RA have shown that these medications are safe, improve glycemia, and carry CV and renal benefits[26].

SGLT2I

SGLT2i act selectively on the sodium-glucose 2 cotransporter in the proximal tubule of the nephron that reabsorbs approximately 90% of filtered glucose, to effectively prevent its reuptake and promote its urinary excretion to reduce blood levels. Glycosuria results whenever filtered glucose exceeds the maximum absorption rate by SGLT2 co-transporters. SGLT2i reduce hemoglobin A1c (HbA1c) by 0.5%-0.7% in an insulin-independent manner with minimal risk of hypoglycemia, leading to weight loss[26]. SGLT2i cause an osmotic diuretic and natriuretic effect that leads to plasma volume contraction, in turn decreasing systolic and diastolic blood pressure (BP) by 4-6 and 1-2 mmHg, respectively[27]. Since filtered glucose load depends on blood glucose, SGLT2i achieve their greatest blood glucose reduction during hyperglycemia. Glucose-lowering efficacy declines from reduced glycosuria as GFR declines. SGLT2i-induced natriuresis leads to increased sodium delivery to the macula densa, and tubular glomerular feedback results in afferent arteriolar vasoconstriction, with reduced intraglomerular hypertension, GFR and albuminuria. Natriuresis-related reductions in BP and possibly renoprotection persist even with reduced kidney function[28]. It should be remembered that KTR still have CKD; the eGFR is often 50 mL/min per 1.73 m^2 or less, and CKD associates with CVD. Therefore, the hypothesis that SGLT2i reduce CV risk in KTR is worth exploring.

SGLT2i are available both individually and combined with metformin and DPP4i. Sotagliflozin is a dual SGLT2/1i for treating both T2DM and T1DM. Sotagliflozin also inhibits intestinal SGLT2, delaying glucose absorption and post prandial glucose rise[29].

Adverse effects of SGLT2i

SGLT2i cause mycotic genital or yeast infections, often with candida species, in about 9%-18% of women with half this rate in men[30-32]. Urinary tract infections (UTI) are less common. Euglycemic diabetic ketoacidosis (DKA), while rare, occurs in the context of insulin deficiency, sudden reductions in insulin dose, or increased dose requirements from illness, surgery or alcohol abuse[12]. The incidence of DKA was increased with dapagliflozin[33], while increased lower limb amputations were seen with canagliflozin[32]. However, a meta-analysis of randomized clinical trials (RCT) found no class effect-based increased risk for amputation[34]. Volume depletion may worsen perfusion of an already dysfunctional vascular network, but this hypothesis remains unproven[35]. Fracture risk may be higher with canaglifozin but this risk was unconfirmed by meta-analysis[36]. SGLT2i may also affect bone metabolism and density[37].

SGLT2i and CV protection

SGLT2i reduce 3-point major adverse CV events [MACE: Death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke], all-cause mortality and HF hospitalizations in the general population in varying combinations[31-33]. SGLT2i significantly reduced MACE in those with established CVD[38]. Potential beneficial mechanisms include naturietic diuresis, reduced inflammation, and increased hematocrit from erythropoietin production with enhanced myocardial tissue oxygen delivery[39].

Several trials specifically examined HF as a primary outcome[38,40-42]. Many patients did not have T2DM, and SGLT2i reduced CV death and HF hospitalization or progression regardless of diabetes status[43,44]. Patients with HFrEF of < 40% showed a significantly lower CV death or HF hospitalization again regardless of T2DM status[44], and a slower eGFR decline in T2DM[45]. With T2DM and recent worsening HF there was lower CV mortality and HF hospitalization.

LVH has not been studied to the same extent as CV mortality and HF. However, a substudy of the EMPA-HEART (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes) CardioLink-6 RCT showed that empagliflozin was associated with significant reduction in LV mass index, possibly from increased red cell mass and improved myocardial tissue oxygen delivery[46].

SGLT2i and kidney protection

Empagliflozin was associated with slower CKD progression, reduced albuminuria progression, and reduced ESKD or death and maintenance[45]. The CANVAS trial using canagliflozin showed a reduced eGFR decline and reduced albuminuria in T2DM[47], while CREDENCE demonstrated both reduced kidney failure and CV events in T2DM[48]. The DAPA-CKD trial of dapagliflozin in CKD with or without T2DM demonstrated a lower composite of sustained decline in eGFR by 50%, ESKD, or death from renal or CV causes[49]. A systematic review and meta-analysis of data from EMPA-REG, CANVAS, CREDENCE, and DECLARE TIMI 58 found that SGLT2i reduced risk of dialysis, acute kidney injury (AKI), and death due to kidney disease in patients with T2DM eGFR levels down to 30 mL/min per 1.73 m^2[50].

A pre-specified meta- analysis of trials involving empagliflozin and dapagliflozin on hospitalisations for HF were consistent, suggesting that they improve renal outcomes, all-cause and CV death in patients with HFrEF[51]. Another meta-analysis showed that SGLT2i improved CV and kidney outcomes, regardless of T2DM, HF, and/or CKD status, with the greatest benefit for HF-related hospitalization and CKD progression[52].

SGLT2i use in KTR with PTDM

KTR are typically excluded from large clinical trials, including registration trials. The safety and efficacy of SGLT2i in non-KT patients with T2DM is now well-established, and so has led to attempts to extend the study of SGLT2i to KTR. A recent systematic review and meta-analysis of 8 studies in 132 KTR showed that SGLT2i were effective in lowering HbA1C and body weight, and preserved kidney function with no serious adverse events such as euglycemic ketoacidosis or acute rejection[53]. Fourteen patients had a UTI, one patient had a myocotic gential infection, one AKI, and one cellulitis. Another recent review concluded that SGLT2i are safe, along with GLP-1 RA and DPP4i, but are not as efficacious as in non-diabetic non-KTR[54].

A small RCT using empagliflozin in 22 KTR (versus 22 placebo) showed that the magnitude of HbA1c reduction depended on eGFR and baseline HbA1c, with no significant difference in adverse events, immunosuppressive drug levels, or eGFR[55]. A pilot study to replace insulin with empagliflozin in 14 stable KTR resulted in weight loss, but also significant drop-out and increased HbA1c, necessitating the reinstitution of insulin therapy in some[56]. SGLT2i were not as efficacious in KTR compared to other diabetic groups, perhaps from lower eGFR and the vasoconstrictive effect of CNI. A case series of 10 KTR demonstrated that the median HbA1c decreased from 7.3% to 7.1%[57]. An uncontrolled study of canagliflozin in 24 KTR, 23 of who were male, showed reduced body weight, BP, HbA1c, and need for other hypoglycemic agents. There were also no hypoglycemic episodes[58]. Other small series have reported similar findings[59]. Another experience using canagliflozin of 10 patients that also included 4 simultaneous pancreas-KT recipients showed that the magnitude of improvements in glycemic control, weight, and BP are similar to nontransplant patients[60]. A search of the Cochrane Kidney and Transplant Register of Studies reported that SGLT2i probably do not affect kidney graft survival compared to placebo, but may improve glycemic control without causing hypoglycemia and

affecting eGFR long-term[61].

Erythrocytosis has been noted with SGLT2i[62]. A well-described adverse event seen in KTR is post-transplant erythrocytosis[63]. Increased erythropoietin production is seen with SGLT2i and may be beneficial in the general population, but whether this is a positive effect in KTR is unknown. Posttransplant erythrocytosis (PTE) occurs in 8%-15% of KTR and affects patients with well-preserved graft function, commonly 8-24 mo post-KT[64]. PTE can cause malaise, headache, lethargy, dizziness, thromboembolic events, and a 1%-2% mortality. Endogenous erythropoietin may play a central role in PTE with a defect in normal feedback regulation, and persistent erythropoietin secretion from native kidneys. PTE is generally treated with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and occasionally phlebotomy[64,65]. A randomized study of empagliflozin for 6 mo in non-KT patients suggested that hematocrit increase is at least partly the result of increased erythropoietin and stimulated erythropoiesis rather than hemoconcentration, based on changes in red blood cell (RBC) morphology, reduced ferritin or iron stores, differential time course of response, and reduced RBC hemoglobin concentration[46]. This safety concern regarding erythrocytosis particularly needs evaluation in KTR.

Dose adjustments of SGLT2i in CKD are recommended (Table 1). Since glucose-mediated hyperfiltration and high blood sugar levels combine to increase glucose filtration[66], the glucose-lowering effects of SGLT2i are decreased at an eGFR < 60 mL/min and almost absent with eGFR < 30 mL/min.

KDIGO guidelines do not currently recommend using SGLT2i in KTR[15]. When used, however, proper patient education is key in reducing the risk of SGLT2i-related complications. Patients should be counseled on sick day management that includes temporarily stopping SGLT2i during periods of illness with vomiting, diarrhea or other states that risk dehydration or intravascular volume depletion. as well as around planned surgical procedures. These illnesses are common early after KT. The eGFR is in a state of flux, with frequent change in kidney function from acute rejection, infections, and CNI-induced vasoconstriction. CNI dose adjustments are frequent. Transplant renal artery stenosis may occur from edema at the anastomotic site, and there is often surgical manipulation of the urinary tract, including stent removal. KTR may also have a pre-existing burden of peripheral vascular disease or recurrent UTI. Peripheral arterial disease may be worsened due to the anastomosis of the kidney allograft to the external iliac artery, further reducing lower extremity arterial perfusion. Peri-transplant ischemic CV events may occur, further affecting effective circulating volume. Post-KT hyperglycemia also commonly improves with routine corticosteroid dose reduction in the first few months after KT, and so new antihyperglycemic medication introduction is often delayed. Diuretics are commonly prescribed early after KT for volume expanded states, especially if heart function is reduced or there is significant peripheral edema. Some patients experience difficulty in unlearning the salt-restricted diet imposed by dialysis. SGLT2 inhibition is natriuretic[66] and may theoretically potentiate the natriuretic action of prescribed diuretics.

In summary, despite the prevalence of meticulously studied endpoints in large clinical trials in the general population, as well as small clinical trials and observational studies in KTR, it remains unclear if the cardiorenal benefits associated with SGLT2i in the general population (with or without DM) will more generally translate to PTDM. There is also presently no reason to use SGLT2i in non-diabetic KTR. Nonetheless, SGLT2i appear to be well-tolerated, but should preferably be avoided in the early post-surgical phase of KT.

GLP-1 RA

The incretin system has become an essential target for managing T2DM. Incretins are hormones produced by the intestinal mucosa in response to oral food intake, and enhance insulin while suppressing glucagon secretion in a glucose dependent manner to lower blood glucose[67-70]. Thus, incretins reduce insulin release when glucose levels are near-normal. Incretin hormones include glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. GLP-1 also slows gastric emptying and increases satiety, leading in-turn to weight loss. Insulin secretion is greater in response to oral than intravenous glucose intake, the so-called "the incretin effect", but this effect decreases in T2DM[70]. The GLP-1 effect declines with impaired insulin secretion, insulin resistance, and hyperglycemia, all leading to decrease in GLP-1 receptor expression and increased GLP-1 resistance[70-72]. GLP-1 RA are eliminated by proteolytic degradation and glomerular filtration, so their metabolism does not involve CYP- or

Table 1 Newer antihyperglycemic agents and chronic kidney disease

CKD stage	1	2	3a	3b	4	5
eGFR (mL/min per 1.73 m^2)	≥ 90	60-89	45-59	30-44	15-29	≤ 15
SGLT2 inhibitors						
Canagliflozin (Invokana)	300 mg OD	Dose adjustment not required	Reduce dose to 100 mg OD if < 60 mL/min	Reduce dose to 100 mg OD in previously treated patients with albuminuria > 33.9 mg/mol. Do not initiate if < 30 mL/min		
Dapagliflozin (Forxiga)	10 mg OD	Dose adjustment not required		Not recommended	Contraindicated	
Empagliflozin (Jardiance)	25 mg OD	Dose adjustment not required			Contraindicated	
Ertugliflozin (Steglatro)	15 mg OD	Dose adjustment not required	Not recommended for initiation of therapy. Discontinue if persistently < 45 mL/min		Contraindicated	
Sotogliflozin (Zynquista)	400 mg OD	Dose adjustment not required	Not recommended for initiation of therapy. Discontinue if persistently < 45 mL/min		Contraindicated; safety not established	
GLP-1R agonists						
Dulaglutide (Trulicity)	1.5 mg weekly	Dose adjustment not required				Caution as safety not established
Exenatide (Byetta)	10 μg BID	Dose adjustment not required	Caution if 30-50 ml/min		Not recommended due to risk of accumulation	
Liraglutide (Victoza)	1.8 mg OD	Dose adjustment not required				Safety not established
Lixisenatide (Adlyxine)	20 μg OD	Dose adjustment not required			Safety not established	
Semaglutide (Ozempic)	1 mg weekly	Dose adjustment not required			Limited experience	Not recommended
Semaglutide (Rybelsus)	14 mg OD	Dose adjustment not required			Limited experience	Not recommended
DPP4 inhibitors						
Alogliptin (Nesina)	25 mg OD	Dose adjustment not required	Reduce dose to 12.5 mg		Reduce dose to 6.25 mg	
Linagliptin (Trajenta)	5 mg OD	Dose adjustment not required				Limited experience
Saxagliptin (Onglyza)	5 mg OD	Dose adjustment not required	Reduce dose to 2.5 mg if < 50 mL/min			Not recommended
Sitagliptin (Januvia)	100 mg OD	Dose adjustment not required	Reduce dose to 50 mg if < 50 mL/min		Reduce dose to 25 mg	
Vildaglitin (Galvus)	50 mg BID	Dose adjustment not required	Reduce dose to 50 mg OD if < 50 mL/min			

CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; SGLT2: Sodium glucose co-transporter 2; GLP-1R: Glucagon-like peptide-1 receptor; DPP4: Dipeptidyl peptidase 4.

transported-mediated drug-drug interactions. GLP-1 RA are incretin mimetics.

Hypoglycemia may occur if GLP-1 RA is given concomitantly with an insulin secretagogue. Most GLP-1 RA are administered subcutaneously, but there is one oral GLP-1 RA available (Table 1). Common adverse effects include nausea, vomiting, diarrhea, and injection-site reactions. GLP-1 RA are contraindicated for patients with a history of medullary thyroid cancer, multiple endocrine neoplasia 2, or pancreatitis. Oral intake must be adequate for GLP-1 RA to be given.

GLP-1 RA, CV, and kidney protection

GLP-1 RA studies were generally conducted in individuals with established atherosclerotic CVD. Except lixisenatide[72], all current GLP-1 RA are associated with a reduction in risk of MACE in patients with T2DM and established CVD. Lixisenatide, liraglutide, and dulaglutide all demonstrated CV safety[72-75].

The LEADER trial using liraglutide that included individuals with eGFR 15-30 mL/min per 1.73 m^2, demonstrated a greater benefit to MACE reduction with eGFR < 60 mL/min[73]. Liraglutide added to standard care resulted in lower new-onset and slower progression of diabetic CKD, driven primarily by persistent macroalbuminuria, with a similar rate of renal adverse events including AKI to placebo. The REWIND trial using dulaglutide showed, besides reduced MACE, a reduction in new severely increased albuminuria, sustained eGFR decline of 30% from baseline, or renal replacement therapy[76]. The AWARD 7 trial of once-weekly dulaglutide in moderate-to-severe CKD produced glycaemic control similar to insulin, with reduced eGFR decline[77]. SUSTAIN 6 CVOT using weekly semaglutide also demonstrated safety and significantly reduced MACE in posthoc analysis for superiority[78]. A systematic review and meta-analysis showed that GLP-1 RA are cardioprotective across many population subgroups, and reduce HF hospitalization and all-cause mortality[79]. In summary therefore, besides CVD risk reduction with GLP-1 RA, there is also risk reduction in new-onset albuminuria, eGFR decline, and progression to ESKD or kidney death.

GLP-1 RA use in KTR with PTDM

GLP-1 RA are recommended by most guidelines as second line as an alternate to an SGLT2i after metformin in managing T2DM especially with CVD, CV risk factors, or CKD. Small case series using GLP-1 RA in KTR do exist, showing no serious adverse effects or immunosuppressive drug interactions[80]. However, the evidence for use in KTR remains very limited. A review of the Cochrane Kidney and Transplant Register found no randomized, quasi-RCT and cross-over studies examining the effects of GLP-1 RA on safety and efficacy for treating pre-existing and new onset diabetes in KTR[61].

The rationale for using GLP-1 RA in KTR is that incretin therapies are able to counterbalance the interference of immunosuppressive drugs on insulin secretion. Corticosteroids are commonly used in anti-rejection regimens for KTR along with CNI (tacrolimus and cyclosporine), all of which affect glucose metabolism by decreasing glucose utilization and enhancing hepatic gluconeogenesis. Corticosteroids also directly decrease insulin secretion and increase insulin resistance. CNI impair α-cell and β-cell function and the incretin effect. The mechanism of action of GLP-1 RA may be ideal in this situation due to their insulinotropic, glucagonostatic and glucose-lowering effects that directly target defects linked to immunosuppressive-induced hyperglycemia[81], although drug interactions such as CNI resulting in increased drug exposure remain a concern[82]. Weight loss is another benefit of GLP-1 RA since weight gain is a common consequence of both hyperglycemia and KT more generally, making GLP-1 RA especially appealing for PTDM.

A study examining the role of hyperglucagonemia in PTDM, and the insulinotropic and glucagonostatic effects of GLP-1 during fasting and hyperglycemic states, concluded that PTDM is characterized by reduced glucose-induced insulin secretion and attenuated glucagon suppression. Moreover, similar to T2DM, GLP-1 infusion reduced glucagon concentration and increased first- and second-phase insulin secretion[82]. A major concern of GLP-1 RA in KTR is delayed gastric emptying, potentially affecting absorption of co-administered narrow therapeutic index medications such as CNI[83]. Although GLP-1 RA are not metabolized by the liver or involved in cytochrome or transporter mediated drug-drug interaction, there may be a delay in drug concentration, but it appears drug exposure may not be affected. Thus GLP-1 RA are theoretically safe, but close monitoring of tacrolimus and cyclosporine concentrations and potential side effects is required. A case series on safety of coadministration of liraglutide and tacrolimus found that tacrolimus $AUC_{0\text{-}12h}$ reduced but trough levels were not affected[80], and there was no evidence of acute rejection.

A chart review of KTR who received liraglutide for glycemic control showed significant improvement in A1C, FBS, eGFR and body weight with minimal side effects[84]. Another retrospective study that included 7 KTR with PTDM receiving GLP-1 RA for 12 mo found no significant changes in tacrolimus concentration or kidney function[85]. A large experience of 63 KTR with PTDM using dulaglutide found sustained reduction in body mass index and insulin requirement for up to 24 mo, without increased risk of cancer, CV events, graft-failure, or all-cause mortality. Gastrointestinal side effects were infrequent and there was no requirement for change in immunosuppressive therapy[86]. A recent study however did not demonstrate weight loss, but did show reduced total daily insulin dose and a low risk of hypoglycemia with no adverse effect on kidney allograft outcomes[87].

DPP4I

DPP4i, otherwise known as gliptins, prevent the inactivation of GLP-1 and GIP. They are once daily drugs with the exception of vildagliptin[88]. Higher levels of endogenous GLP-1 enhance incretin action including glucose-dependent insulin secretion. They slow gastric emptying, increase satiety, and reduce postprandial glucagon secretion. DPP4i are generally well tolerated, have a low risk for hypoglycemia, and are weight neutral, but can cause acute pancreatitis[88].

DPP4i, CV, and kidney protection

All major CV trials of DPP4i including linagliptin[89], sitagliptin[90], saxagliptin[91], and alogliptin[92] revealed non-inferiority compared to placebo for the risk of major events. Non-inferiority was also evident when linagliptin was compared to glimepiride[93]. However, in the SAVOR-TIMI 53 trial, saxaliptin was associated with an increased risk of hospitalization for HF in patients with elevated N-terminal pro B-type natriuretic peptide levels, a history of HF, or CKD with eGFR < 60 mL/min[94]. Linaglipitin and saxagliptin reduce the risk for albuminuria progression, or even improve albuminuria, regardless of baseline eGFR[95,96]. This benefit was not demonstrated with sitagliptin[97]. The KDIGO 2020 guidelines highlight the role of DPP4i in T2DM and CKD. Therefore, while DPP4i may be useful adjuncts to control blood glucose and favorably affect albuminuria at best, their effect on CVD outcomes and CKD progression remains uncertain.

DPP4i use in KTR with PTDM

Most diabetes practice guidelines such as those of Diabetes Canada and KDIGO recommend DPP4i as add-on therapy for patients without CVD in whom glycemic targets are not achieved, especially if a lower risk of hypoglycemia and/or weight gain are priorities. A systematic review and meta-analysis of 5 studies in KTR with PTDM found that DPP4i improved glycemic control compared to either placebo or other oral anti-hyperglycemic agents, but did not significantly affect eGFR or tacrolimus concentration[98]. A meta-analysis including eight DPP4i studies showed both efficacy and safety[99]. A search of the Cochrane Kidney and Transplant Register[61] described the evidence concerning DPP4i as being of low to very low certainty. A study of 65 KTR demonstrated increased cyclosporine concentrations with sitagliptin but not linagliptin[100].

CONCLUSION

Safety data for SGLT2i, GLP-1 RA, and DPP4i are reassuring, and the CV and kidney risk reduction benefits are certainly substantial for SGLT2i and GLP-1 RA in non-KTR with T2DM. GLP-1 RA do not share benefits similar to SGLT2i with respect to preventing HF. GLP-1 RA are a potential treatment option for PTDM to help offset the increased CV risk associated with KT. Incretin therapy uniquely counteracts the interference of immunosuppressants on insulin secretion. DPP4i are useful for glycemic control. The first priority in managing KTR is achieving glycemic control; any CV and kidney benefits should be considered incidental at this time.

More RCT are needed to support using all three drugs in KTR. The UTI risk with SGLT2i may be especially concerning for KTR. With a single kidney, volume sensitivity may theoretically risk AKI, and so sick day management education is critical. SGLT2i, GLP-1 RA, and DPP4i may eventually prove to be ideal choices for both glycemic control and cardiorenal protection in KTR, but the evidence in KTR for now remains limited. The risk of intravascular volume depletion, brought on by the use of diuretics, renal artery stenosis, and diarrhea due to mycophenolic acid may compound the concern for AKI. Sick day management of other drugs is already prescribed to KTR. Dialysis patients also need to unlearn their salt restricted diet. Other potential concerns in KTR include worsening post-transplant osteoporosis, with most bone loss occurring early after KT. KTR may also carry a burden of peripheral vascular disease, occasionally worsened by the anastomosis of the kidney allograft to the external iliac arterial system. The hemoglobin should be monitored. These special considerations are described in Table 2. However, there is no reason that any of the newer antihyperglycemic drugs cannot be used in KTR as long as patients are carefully monitored. The early studies involving KTR are all generally favorable.

Table 2 Special considerations in prescribing newer antihyperglycemic agents to kidney transplant recipients

Clinical evidence	Largely observational
Kidney function	Reduced glomerular filtration rate
	Fluctuating glomerular filtration rate
	Post-transplant diuresis
Surgically altered urinary tract	Urinary tract infections
Graft arterial anastomosis	Peripheral vascular disease
Immunosuppression	Fluctuating glucose control
	Interaction with calcineurin inhibitors
	Urinary tract infections
Gastrointestinal upset	Intravascular volume depletion
	Dehydration
Others	Post-transplant erythrocytosis

In summary, initial evidence seems to indicate that newer antihyperglycemic agents can be used in KTR. It may be preferable to avoid these drugs in the first 6 mo after KT due to the increased frequency of infections typically seen from enhanced immunosuppression coupled with an anatomically altered urinary tract, as well as susceptibility to intravascular volume depletion and the volume sensitivity of a solitary kidney. These drugs should not be considered first-line agents, but can be prescribed cautiously in the context of poor glycemic control after other suitable measures specific to KTR have already been undertaken.

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