i) **Sweet and Simple as Syrup: A Review and Guidance for Use of Novel Antihyperglycemic Agents for Post-Transplant Diabetes Mellitus and Type II Diabetes Mellitus After Kidney Transplantation**

Abbreviated title: Review of novel anti-hyperglycemic agents following kidney transplant

Key words: Kidney transplantation, SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor, diabetes mellitus

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Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract Page

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Sweet and Simple as Syrup: A Review and Guidance for Use of Novel Antihyperglycemic Agents for Post-Transplant Diabetes Mellitus and Type II Diabetes Mellitus After Kidney Transplantation

Clin Transplant

Abbreviations

Type 2 diabetes mellitus (T2DM), post-transplant diabetes mellitus (PTDM), sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1RA), dipeptidyl peptidase IV inhibitors (DPP4i), kidney transplant recipients (KTR), grading of recommendations assessment, development and evaluation (GRADE), new onset diabetes after transplant (NODAT), Hemoglobin A1c (HbA1c), oral glucose tolerance test (OGTT), blood glucose (BG), calcineurin inhibitors (CNI), human leukocyte antigen (HLA), American Diabetes Association (ADA), solid organ transplant (SOT), Kidney Disease: Improving Global Outcomes (KDIGO), estimated glomerular filtration rate (eGFR), 3-point major cardiovascular events outcome (MACE), randomized controlled trials (RCT), Atherosclerotic Cardiovascular Disease (ASCVD), Heart failure (HF), Ejection Fraction (EF), Heart Failure with Reduced Ejection Fraction (HFrEF), Cardiovascular (CV)), Blood Pressure (BP), Renal Replacement Therapy (RRT), Serum Creatinine (SCr), U.S Food and Drug Administration (FDA), Chronic Kidney Disease (CKD), Multiple endocrine neoplasia syndrome (MEN2), End stage renal disease (ESRD), gastrointestinal (GI), Creatinine Clearance (CrCl), kilograms (kg), cardiovascular outcomes trials (CVOTs), cardiovascular disease (CVD), United States (US), interquartile range (IQR), heart failure (HF), myocardial infarction (MI), systolic blood pressure (SBP), low-density lipoprotein (LDL), triglyceride (TG), diabetes mellitus (DM), week (wk), not applicable (N/A), post-transplant lymphoproliferative disorder (PTLD), headache (HA), urinary tract infection (UTI), simultaneously pancreas/kidney transplant recipient (SPKTR), acute kidney injury (AKI), not reported (NR), urine protein: creatine ratio (UP/CR), antibiotic prophylaxis (abx ppx), standard deviation (SD), biopsy proven acute rejection (BPAR), diabetic ketoacidosis (DKA), discontinue (d/c), not significant (NS), fasting blood glucose (FBG), liver transplant (LT), body mass index (BMI)

Conflicts of Interest

No authors have any conflicts of interest to disclose

ABSTRACT

Uncontrolled type 2 diabetes mellitus (T2DM) and post-transplant diabetes mellitus (PTDM) increase morbidity and mortality after kidney transplantation. Conventional strategies for diabetes management in this population include metformin, sulfonylureas, meglitinides and insulin. Limitations with these agents, as well as promising new antihyperglycemic agents, create a need and opportunity to explore additional options for transplant diabetes pharmacotherapy. Novel agents including sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1RA), and dipeptidyl peptidase IV inhibitors (DPP4i) demonstrate great promise for T2DM management in the non-transplant population. Moreover, many of these agents possess renoprotective, cardiovascular, and/or weight loss benefits in addition to improved glucose control while having reduced risk of hypoglycemia compared with certain other conventional agents. This comprehensive review examines available literature evaluating the use of novel antihyperglycemic agents in kidney transplant recipients (KTR) with T2DM or PTDM. Formal grading of recommendations assessment, development, and evaluation (GRADE) system recommendations are provided to guide incorporation of these agents into post-transplant care. Available literature was evaluated to address the clinical questions of which agents provide greatest short- and long-term benefits, timing of novel antihyperglycemic therapy initiation after transplant, monitoring parameters for these antihyperglycemic agents, and concomitant antihyperglycemic agent and immunosuppression regimen management. Current experience with novel antihyperglycemic agents is primarily limited to single-center retrospective studies and case series. With ongoing use and increasing comfort, further and more robust research promises greater understanding of the role of these agents and place in therapy for kidney transplant recipients.

Key words: Kidney transplantation, SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor, diabetes mellitus

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INTRODUCTION

Hyperglycemia after transplantation was first described by Dr. Thomas Starzl in 1964.[1] Various terms have been used to describe hyperglycemia following transplant such as steroid-induced diabetes or new onset diabetes after transplant (NODAT). However, in 2013 an international consensus of transplant nephrologists, surgeons, clinical scientists, and diabetologists favored the term post transplantation diabetes mellitus (PTDM). PTDM should be applied in the setting of newly diagnosed diabetes mellitus after transplant as opposed to type 2 diabetes mellitus (T2DM), which is diagnosed prior to transplant. Transient hyperglycemia due to high doses of corticosteroids and postoperative stress occurs frequently in the immediate post-transplant period and therefore diagnosis of PTDM should be considered only after being on a stable immunosuppressive regimen without acute infection.[2,3] The criteria for diagnosis of PTDM are similar to that of T2DM in the general population [two of the following: Hemoglobin A1c (HbA1c) ≥6.5%, random fasting blood sugar ≥ 126 mg/dL, 2 hour post oral glucose tolerance test (OGTT) ≥ 200 mg/dL, or random blood glucose (BG) of ≥ 200 mg/dL with symptoms of hyperglycemia such as polyuria and polydipsia].[4] HbA1c may be inaccurate in the first 3 months following transplant due to confounding issues, such as blood transfusions during transplant surgery. Similar to other forms of diabetes mellitus, ongoing monitoring for hyperglycemia management, with HbA1C every three to six months is recommended. In addition to the classic risk factors for T2DM, there are several transplant-specific factors that lead to development of PTDM. These include the use of immunosuppressive agents [e.g., calcineurin inhibitors (CNI) and corticosteroids], allograft rejection, infections, donor characteristics and human leukocyte antigen (HLA) mismatches/specific HLA alleles.[5,6] Between 2010-2020, the number of

individuals with diabetes mellitus awaiting kidney transplant rose from 42 to 47%. While the incidence of PTDM is high at 15%, new data shows that it is declining due to changing paradigms in titration of CNI and corticosteroids.[7,8] Early and accurate detection is vital as diabetes mellitus and PTDM are associated with increased mortality and morbidity.[9–16]

Management of PTDM is similar to that of T2DM in the general population with a focus on strict glycemic control and reduction in the occurrence of diabetes-related complications. Several new anti-hyperglycemic agents have been introduced since 2005: GLP1RA, DPP4i, and SGLT2i. The American Diabetes Association (ADA) guidelines recommend the use of GLP1RA and SGLT2i in patients with high risk of atherosclerotic cardiovascular disease.[17] In addition, SGLT2i have shown to have renoprotective effects as demonstrated in multiple large trials.[18] See Table 1 for details highlighting the use of these agents in the general population.

During the first 1-2 months post kidney transplant, whilst significant changes are occurring to the immunosuppressive regimen and renal function, hyperglycemia is usually treated with insulin. It is hypothesized that early use of insulin resulted in beta cell protection thereby reducing glucotoxicity and the occurrence of PTDM.[19] In mouse models, metformin has been shown to improve CNI-induced hyperglycemia as well as improve glucose intolerance caused by sirolimus.[20,21] Although metformin is used as a treatment for PTDM, safety data in solid organ transplant (SOT) recipients is lacking. Short-term studies have demonstrated safety of the use of glinides following kidney transplant.[22,23] The 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends for use of metformin for KTR with PTDM with an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2.[24,25] The ADA Standards for Medical Care in Diabetes in 2017 added a specific section for PTDM, although specific treatment recommendations were not provided.[26] Overall, there has been a dearth of clinical trials evaluating the effects of the newer antihyperglycemic agents following kidney

transplant. The advent of these agents that offer improved glycemic control, reduction in 3-point major cardiovascular events outcomes (MACE; comprised of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), renoprotective effects and weight loss is exciting and promising by providing additional options for effective management of PTDM. Practice guidelines for the novel antihyperglycemic agents in the post-transplant setting are lacking. This comprehensive review discusses the available literature and provides evidence-based recommendations on the use of these novel antihyperglycemic agents, for treatment of PTDM in KTR. Given that many studies included both patients with PTDM and those with T2DM diagnosed prior to transplantation, this review also provides insight for the management of T2DM in KTR as well.

METHODS

Study Selection

For this review of the English literature, PubMed database searches were conducted to identify relevant studies published prior to September 1, 2022. The search terms used for the literature review were:

(SGLT2 OR sodium glucose co-transporter 2 inhibitor OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin) AND (kidney transplant OR post transplant diabetes mellitus OR new onset diabetes after transplant)

(GLP1 OR glucagon-like peptide-1 receptor agonist OR albiglutide OR semaglutide OR exenatide OR dulaglutide OR liraglutide OR lixisenatide) AND (kidney transplant OR post transplant diabetes mellitus OR new onset diabetes after transplant)

(DPP4 OR dipeptidyl peptidase IV inhibitor OR saxagliptin OR sitagliptin OR alogliptin OR vildagliptin OR linagliptin) AND (kidney transplant OR post transplant diabetes mellitus OR new onset diabetes after transplant)

All randomized controlled trials (RCT), case series, cohort studies were included if study population included adults who had received a renal transplant with a diagnosis of either pre-transplant T2DM or PTDM or NODAT. Case reports were excluded.

Level of Evidence and Strength of Recommendation Assessment Methods

Authors provided a level of evidence assessment and assigned a strength of recommendation designation for each of the major clinical questions concluding the review. The GRADE system was utilized to rate the level of evidence as High (A), Moderate (B), Low (C), or Very Low (D) and strength of recommendation as Strong (1) or Weak (2).[27–32] Quality of evidence was assigned as High (A) if further research was unlikely to change confidence in estimated effect; Moderate (B) if further research was likely to impact confidence in estimated effect; Low (C) if further research was very likely to impact confidence in estimated effect; and Very Low (D) if further research was needed to identify an estimation of effect. Strength of recommendation was designated as strong (1) if there was high quality of evidence available (e.g., well-designed randomized controlled trials) and there was confidence that benefit outweighed risk. Strength of recommendation was designated as weak (2) if there was lower quality of evidence (e.g., case series, retrospective cohort studies) and uncertainty about whether benefit outweighs risk.

Evidence was reviewed by the primary author who developed recommendations, assessed level of evidence, and assigned strength of recommendations. All content was then reviewed by an additional author to validate. The full author group reviewed all recommendations and quality of evidence for consensus. Where discrepancy existed, group discussion was used to reach agreement.

Table 1. Benefit and Risk Summary of Novel Antihyperglycemic Agents Available in the United States in General Population (2022)[24,47-50,63-68,80]

Class	ASCVD	Heart Failure	Renal Disease	Weight Loss	Safet
LP1RA	Minimizes risk factors (weight loss) Dulaglutide, Liraglutide, Semaglutide may lower CV events and mortality Exenatide XR, Lixisenatide: neutral	Neutral	Modest reduction in albuminuria Glucose lowering effect is lower at lower eGFR	Significant Benefit Greatest weight loss: Semaglutide > Liraglutide > Dulaglutide, Lixisenatide, Exenatide XR	Hypoglycemic but may decrea dose if adc concomitant GI effects: (>10%), a pancreatitis
GLT2i	Minimizes risk factors (weight loss, BP) All shown to reduce CV mortality and events	Reduces risk of HF hospitalization Dapagliflozin has FDA indication for HFrEF Empagliflozin has FDA indications for HF regardless of EF	Significant reduction in albuminuria All carry FDA indications for CKD Glucose lowering effect is lower at lower eGFR	Moderate Benefit Modest weight loss	Hypoglycemic GI Effects: M Infection risk: 10%) Metabolic risk ketoacidosis symptomatic depletion (hyp syncope, dehy
DPP4i	Neutral	Saxagliptin may increase risk for HF hospitalization	Neutral	No Benefit Weight neutral	Hypoglycemic GI: Increased lipase) (1 – 10 pancreatitis

Abbreviations: Atherosclerotic Cardiovascular Disease (ASCVD), Heart failure (HF), Ejection Fraction (EF), Heart Failure with Reduced Ejection Fraction (HFrEF), Cardiovascular (CV), Estimated Glomerular Filtration Rate (eGFR), Blood Pressure (BP), Renal Replacement Therapy (RRT), Serum Creatinine (SCr), U.S Food and Drug Administration (FDA), Chronic Kidney Disease (CKD), Gastrointestinal (GI), nausea, vomiting, and diarrhea (N/V/D)

Table 2. Overview of Novel Antihyperglycemic Agents[33–45]

<table>
<tr><th>Class</th><th>Use Criteria:</th><th>Dosing:</th></tr>
<tr><td>GLP1RA</td><td>Route:

Subcutaneous injection and oral

Do not start if yes to any of the following:
• Personal or family history of medullary thyroid carcinoma
• Multiple endocrine neoplasia syndrome
• Acute or previous history of pancreatitis
• Desire to become pregnant
• On DDP4i (may start if stopping DPP4i)

Note:
• End stage renal disease: use with caution due to limited clinical evidence
• The presence of current GI symptoms secondary to mycophenolate products or other causes may preclude starting</td><td>
<table>
<tr><th>Agents</th><th>Dosing regimen</th><th>Dosing Pearls</th></tr>
<tr><td>Dulaglutide weekly injection</td><td>0.75 mg weekly, may increase to 1.5 mg once weekly after 4-8 weeks if needed. May further titrate to 3 mg after at least 4 weeks at 1.5 mg and then to a max of 4.5 mg weekly after 4 weeks on 3 mg</td><td>No dose adjustment in renal impairment – use with caution</td></tr>
<tr><td>Semaglutide weekly injection</td><td>0.25 mg weekly for 4 weeks, then increase to 0.5 mg weekly; may increase to 1 mg weekly after additional 4 weeks followed by 2 mg weekly after 4 weeks if needed for further control</td><td>Initial 0.25 mg dose is intended to reduce GI symptoms and does not provide effective glycemic control

No dose adjustment in renal impairment – use with caution</td></tr>
<tr><td>Exenatide ER weekly injection</td><td>2 mg once weekly</td><td>eGFR <45 ml/min/1.73 m^2 use is not recommended</td></tr>
<tr><td>Liraglutide daily injection; also available as combination product with</td><td>0.6 mg SQ daily x 1 week, then increase to 1.2 mg daily. If further response needed after</td><td>0.6 mg is intended to reduce GI symptoms and does not provide effective glycemic</td></tr>
</table>
</td></tr>
</table>

	• Upon initiation with concomitant insulin and other antidiabetic agents, closely monitor for hypoglycemia and decrease other agents as needed Counselling tips for GI upset: • Titrate dose slowly • Confirm patient taking prescribed dose before considering dose reduction/therapy failure • Avoid high fat meals, spicy foods, alcohol • Eat smaller, more frequent meals • Consider switching to one weekly agent	insulin degludec	additional week then may increase to 1.8 mg daily	control No dose adjustment in renal impairment – use with caution
		Lixisenatide daily injection; also available as combination product with insulin glargine	10 mcg daily x 14 days then on day 15 increase to 20 mcg daily (maintenance dose)	eGFR <15 mL/minute/1.73 m^2: Use is not recommended
		Exenatide IR twice daily injection	5 mcg twice daily within 60 minutes prior to the two main meals of the day (least 6 hours apart). May increase to 10 mcg twice daily after 1 month if needed for further control	CrCl <30 ml/min not recommended
		Semaglutide oral once daily	3 mg daily x 30 days, then increase to 7 mg daily; may increase to 14 mg after 30 days if needed for further control Administer ≥30 minutes before the first food, beverage, or other medications	3 mg dose is intended to reduce GI symptoms, it does not provide effective glycemic control No dose adjustment in renal impairment – use with caution
SGLT2i	Route: Oral	Dapagliflozin	Initial: 5 mg once daily; may increase to 10 mg once	eGFR <25 mL/minute/1.73 m^2: initiation not recommended, may continue

	Do not start if yes to any of the following: • Dialysis • Active infection • History of recurrent urinary tract infections, genital mycotic infections Note: • SGLT2i should be used cautiously and only under close supervision in those with known risk factors or predisposing conditions for UTIs such as a history of recurrent UTIs, urinary retention, voiding dysfunction, urethral strictures, urinary obstruction, neurogenic bladder dysfunction, or catheterization • Use caution in patients at risk of volume depletion or hypotension; consider decreasing diuretics or antihypertensive medications and encouraging appropriate hydration • Be aware of the risk of euglycemic diabetic ketoacidosis, typically best to avoid		daily after 4 to 12 weeks if needed to achieve glycemic goals	use if already on
		Empagliflozin	Initial: 10 mg once daily; may increase to 25 mg once daily after 4 to 12 weeks if needed to achieve glycemic goals	eGFR <30 mL/minute/1.73 m^2: In patients previously established, some continue use at 10 mg once daily as a treatment for diabetic kidney disease; renal and heart failure benefits have been shown in patients with an eGFR ≥20
		Canagliflozin	Initial: 100 mg once daily prior to first meal of the day; may increase to 300 mg once daily after 4 to 12 weeks if needed to achieve glycemic goals	eGFR <60 mL/minute/1.73 m^2: 100 mg once daily. eGFR <30 mL/minute/1.73 m^2 with: initiation not recommended, however, patients previously established may continue 100 mg once daily 300 mg dose ay cause increased serum potassium, use caution in impaired renal function, and other medications that may increase K

	as monotherapy in patients who are uncontrolled	Ertugliflozin	Initial: 5 mg once daily; may increase to 15 mg once daily after 4 to 12 weeks if needed to achieve glycemic goals	eGFR <45 mL/minute/1.73 m^2: Use is not recommended
DPP4i	Route: Oral Do not start if yes to any of the following: • Heart failure (HF): saxagliptin • Abnormal transaminases: alogliptin • History of pancreatitis • Already on GLP1RA Note: Linagliptin does not require renal dose adjustment	Sitagliptin	100 mg daily	eGFR ≥30 to <45 mL/minute/1.73 m^2: 50 mg once daily eGFR <30 mL/minute/1.73 m^2: 25 mg once daily
		Saxagliptin	2.5-5 mg daily	eGFR <45 mL/minute/1.73 m^2: 2.5 mg once daily
		Linagliptin	5 mg daily	No renal dose adjustment required
		Alogliptin	25 mg daily	CrCl ≥30 to <60 mL/minute: 12.5 mg once daily CrCl <30 mL/minute: 6.25 mg once daily

RESULTS

GLP1RA Agents

Overview in General Population

GLP1RA agents stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, increase satiety, and slow gastric emptying. All agents in this class effectively reduce HbA1c

by approximately 1-2% in the general population, and their effects on weight loss are more variable between 2-6 kilograms (kg) depending on agent and dose.[46] The risk of hypoglycemia is low because their mechanism is glucose-dependent, but may occur if given in conjunction with other antihyperglycemic agents (Table 2).

In addition to the efficacy on glycemic control and weight loss, GLP1RA have demonstrated cardiorenal benefits compared to placebo in the cardiovascular outcomes trials (CVOTs).[17,46,47] Long-acting GLP1RA (albiglutide, dulaglutide, liraglutide, and subcutaneous semaglutide) reduced the risk of MACE, and liraglutide and oral semaglutide also demonstrated cardiovascular mortality benefits. In the CVOTs, renal outcomes were secondary endpoints or not measured. As a class, GLP1RA reduce the incidence of new-onset macroalbuminemia.[46] Based on the results of CVOTs, the international practice guidelines recommend that T2DM patients with Atherosclerotic Cardiovascular Disease (ASCVD) or at high risk for cardiovascular disease (CVD), or chronic kidney disease (CKD) should be treated with an SGLT2i or GLP1RA with proven CVD benefit, either as add-on to metformin or as monotherapy if intolerant to metformin (Table 1).[17,24,47–49]

GLP1RAs are contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome. Two main concerns surrounding the use of GLP1RA in KTR are renal function and gastrointestinal (GI) side effects. There is limited experience with most GLP1RA in patients with severe renal impairment; in particular, exenatide IR, exenatide ER, and lixisenatide should be avoided in patients with creatinine clearance (CrCl) < 15-45 ml/min (Table 2). In the general population, 10-45% of patients receiving GLP1RA experience GI symptoms including nausea, vomiting, and diarrhea, which are also a common reason for early drug discontinuation. Greater than 90% of KTR receive tacrolimus and mycophenolate for initial maintenance immunosuppression, both of which are well known to cause GI side effects primarily diarrhea in approximately 40% of users.[7] Hence, kidney allograft dysfunction and preexisting GI

issues may preclude the initiation of GLP1RA in certain KTR. After initiation, slow dose escalation of GLP1RA is recommended to mitigate the risk of GI side effects.

Literature Summary in Kidney Transplant

Search terms resulted in 201 results, with nine articles meeting the review criteria on GLP1RA use for the management of T2DM or PTDM in KTR (Table 3). Four articles included other SOT recipients and reported the results in aggregates. All articles were single-center retrospective observational studies. Prospective comparative interventional trials of GLP1RA have not been reported in this population. The most commonly assessed GLP1RA was dulaglutide (N=8), followed by liraglutide (N=7), semaglutide (N=4) and exenatide (N=3). One group published their experience with dulaglutide and later compared the same data to liraglutide.[50,51] In all studies, GLP1RA were add-on therapy to the existing insulin or oral antidiabetic agents. Among seven studies that included timing of GLP1RA initiation, the median/mean times from transplant to the initiation of GLP1RA were ≥ 2 years in six studies, and the earliest time to initiation was mean of 11 months post-transplant.[50–56] The duration of follow-up ranged from 3 months to 24 months.

All nine studies reported the changes in HbA1c and weight from baseline to last follow-up. A modest HbA1c reduction of 0.5-2% was observed in four studies, whereas no significant change in HbA1c was found in the other five studies. This inconsistency in glucose lowering efficacy may be due to the heterogeneity of baseline HbA1c among the studies. The largest reduction in HbA1c (from 10.04±1.61% to 8.14±0.83%, p=0.047) was observed by Liou et al. whose study cohort had poorly controlled T2DM at baseline.[57] Variable weight loss of 0.2-9.9 kg was observed in seven studies with no significant changes in the remaining two studies.[50–53,55–58] Since diabetic nephropathy is a progressive disease, it was not possible to assess renoprotective effects of GLP1RA without adequate control arms. In eight studies that included eGFR, either no significant changes or slight improvements from baseline were reported.[50–53,55–58] Of note, no study reported worsening eGFR on

GLP1RA therapy. Three studies included data on proteinuria, with no change in two studies and a decrease in one study.[53,55,58]

Consistent with the general population data, GI symptoms were the most commonly observed side effects, followed by injection site pain. Hypoglycemia was observed as most patients were on other antidiabetic medications, and severe hypoglycemia was not common. Kukla et al. and Sweiss et al. observed pancreatitis in 5.9% and 4.2% of their study cohorts, respectively.[52,55] Since many studies excluded patients who did not continue GLP1RA therapy, the rates for drug discontinuation cannot be accurately assessed from the available literature. A total of 20 patients were reported discontinuing GLP1RA due to GI symptoms (N=9), non-specified adverse effects (N=4), cost (N=2), headache/dizziness/rhinorrhea (N=1), weakness (N=1), pancreatitis (N=1), pancreatic cancer (N=1), and uncontrolled DM (N=1). No specifics regarding concomitant immunosuppression agents on GI symptoms were mentioned.

Seven studies reported the need to reduce concomitant insulin dose and/or oral antidiabetic agents after GLP1RA initiation.[50,51,53,56,58] The mean reduction in insulin dose ranged from 4 unit/day up to 30 unit/day across the studies. Particularly in Kim et al. study, replacing prandial insulin of 20.5±8.4 unit/day with dulaglutide was effective for glycemic control over 6 months (HbA1c 7.0% vs. 7.1%, p=0.53 and fasting glucose 145.43 mg/dL vs. 123.62 mg/dL, p=0.03) and decreased the basal insulin dose from 24.76 unit/day to 15.24 unit/day (-9.52 unit/day, p<0.001).[54] There has been some concern that GLP1RA-induced gastric emptying delay may affect tacrolimus exposure.[59] While tacrolimus or CNI doses were lowered to maintain levels in two studies, four studies observed no significant effects on tacrolimus levels with GLP1RA therapy.[53–58] Putting these together, the impact of GLP1RA on tacrolimus levels seems minimal and manageable by therapeutic drug monitoring. Rejection episodes and patient deaths were reported in two studies; however, the authors did not comment on the association with GLP1RA therapy.[50,52]

GLP1RA Summary

The literature on the use of GLP1RA in KTR was limited to retrospective studies without controls. The effects on HbA1c and weight, as well as GI side effects, with GLP1RA in KTR were comparable to that in the general patient population. In KTR on concomitant insulin therapy, a significant reduction in insulin dose is anticipated after the initiation of GLP1RA and glucose levels should be closely monitored to avoid hypoglycemia. CNI exposure seems to be minimally impacted by GLP1RA therapy, but CNI therapeutic drug monitoring appears to be warranted. There was no study evaluating effects on cardiovascular outcomes.

Table 3. Summary of GLP1RA Studies Included in Analysis

Study	Type, location	Follow up (m)	Treatment arm(s) (N)	Patient population	Baseline eGFR & HbA1c	Time from TXP	Results: HbA1c, eGFR, weight, AE, Discontinued TXT	Comments
Sweiss et al, 2022[52] (N=118)	Retrospective, single-center US	3-12	Dulaglutide (N=45 Liraglutide (N=36) Semaglutide (N=32) Exenatide ER (N=5)	Inclusion • 18 years • SOT recipients with preexisting T2DM or PTDM • GLP1RA therapy 3 months • HbA1c between 3-12 months of GLP1RA therapy Exclusion: • No follow-up • Nonadherence to GLP1RA	eGFR • Median 55 ml/min (IQR 46-66) HbA1c • Median 8% (IQR 7-9)	Median 1029 days (IQR 480-2365)	• HbA1c: ↓ (nadir HbA1c) • eGFR: ↑ • Weight:↓ AEs: • Nausea/vomiting (12; 10%) • Hypoglycemia (9; 7.1%) • Pancreatitis (5; 4.2%) • Diarrhea (4; 3.4%) • 2 discontinued due to AE	• Other outcomes: Insulin dose ↔ HF (3), stroke (1), MI (0), rejection (3), graft dysfunction (1), transaminitis (1) • Kidney 70.3%, liver 19.5%, lung 6.8%, kidney-liver (2.5%), kidney-pancreas (0.8%)
Vigara et al, 2022[53] (N=40)	Retrospective, single-center Spain	6 (N=40); 12 (N=26)	Semaglutide (47.5%) Liraglutide (32.5%) Dulaglutide (20%)	Inclusion • Stable KTR with DM • GLP1RA therapy for 6 months Exclusion: • Follow-up <6 months • Discontinued GLP1RA	eGFR • Mean 46.1±15.2 ml/min/1.73 m^2 HbA1c • Median 7.7% (IQR 6.8- 8.1)	Median 24 months (IQR 15-61)	Efficacy at 6-month follow-up (N=40) • HbA1c: ↓ • eGFR: ↔ • Weight: ↓ Efficacy at 12-month follow-up (N=26) • HbA1c: ↓ • eGFR: ↑ • Weight: ↓ Safety (N=50) • AEs 12; mainly N/V, improved after dose reduction. Discontinued/excluded (2) • Pancreatic cancer (1)/discontinued	• 50 screened, 10 excluded • Preexisting diabetes (N=34), PTDM (N=16) • 2 patients who discontinued GLP1RA for GI were excluded in the outcome analysis. • Other outcomes: tacrolimus levels ↔, insulin dose ↓, proteinuria ↓, SBP ↓, cholesterol ↓ (6m), LDL ↔, TG ↔

Yuguer os Gonzál ez et al, 2021[58] (N=15)	Retrospe ctive, single-center Spain	12	Semaglutide (N=7) Liraglutide (N=4) Dulaglutide (N=2) Empagliflozin (N=2)	Inclusion • KTR >18 years • GLP1 and/or SGLT2i therapy Exclusion: N/A	Scr • Median 1.3 mg/dl (IQR 0.9-1.6) HbA1c • Median 6.7% (IQR 5.8- 8.2)	Not reported	• HbA1c: ↔ • eGFR: ↔ • Weight: ↓ • A few minor AEs in 2 patients (no detail) • 2 discontinued (1 empagliflozin due to UTI requiring hospitalization, 1 GLP1RA due to general weakness)	• GLP1 RA (N=13) + SGLT2i (N=2) • 5 non-DM for weight loss included (about -7 kg loss) • Preexisting DM (N=4), PTDM (N=6), non-DM/obesity (N=5) • Other outcomes: tacrolimus levels ↔, insulin dose/oral meds in 7 DM ↓ (not quantified), proteinuria ↔
Kim et al, 2020[54] (N=37)	Retrospe ctive, single-center South Korea	6	Dulaglutide 0.75 mg/wk (N=17) or 1.5 mg/wk (N=20)	Inclusion • KTR with T2DM • Switched prandial insulin to dulaglutide • Continued dulaglutide 6 months Exclusion: • Not receiving multiple daily insulin • ESRD due to other than DM • Follow-up <6 months • Missing values • Hospitalizatio n • Discontinued dulaglutide due to AE	eGFR • Mean 71.7±18.5 ml/min/1.73 m^2 HbA1c • Mean 7.0±0.9%	10.6±7.5 months	• HbA1c: ↔ • eGFR: Not reported • Weight: ↓ • Nausea (4), vomiting (1), abdominal distention (1), diarrhea (2), injection site pain (1), hypoglycemia (3), no severe hypoglycemia/hospitalizatio n • N/A (Out of 68 screened, 2 patients discontinued dulaglutide due to AE and were excluded.)	• 68 screened; 31 excluded • Out of 68 screened, 2 patients discontinued dulaglutide due to AE and were excluded. • Other outcomes: mean CNI doses were lower at 6 months, basal insulin dose ↓
Kukla et al, 2020[55] (N-17)	Retrospe ctive, single-center US	≥ 12 (N=14)	Liraglutide (N=14) Dulaglutide (N=2) Exenatide (N=1)	Inclusion • 18 years • KTR with preexisting T2DM or PTDM • Follow-up 1 month after GLP1RA initiation Exclusion: N/A	eGFR • Median 53 ml/min/1.73 m^2 (IQR 40.2-60) HbA1c • Median 7.7% (IQR 6.6-8.1)	Median 3.9 years (IQR 1.0-9.9)	• HbA1c: ↔ • eGFR: ↔ • Weight: ↔ • AEs: Only reported as reasons for discontinuation (4) • 5 discontinued (3 GI, 1 pancreatitis, 1 uncontrolled DM)	• Kidney (N=14), kidney-heart (N=2), kidney-liver (N=1) • Preexisting T2DM (N=3), PTDM (N=11) • Other outcomes: tacrolimus doses ↔ insulin dose ↓ proteinuria ↔
Thanga velu et al, 2020[56] (N=19)	Retrospe ctive, single-center US	12	Liraglutide (N=10) Dulaglutide (N=5) Semaglutide (N=2) Exenatide (N=2)	Inclusion • SOT recipients with preexisting T2DM or PTDM • GLP1RA therapy post-txp • HbA1c between 3-12 months of GLP1RA	eGFR • Median 55 ml/min (IQR 46-66) HbA1c • Median 8.0% (range 4.6-10.8)	Median 60 months	• HbA1c: ↔ • eGFR: ↔ • Weight: ↓ • Most common AE: nausea (N=5). No severe hypoglycemia, pancreatitis, or malignancy • 5 discontinued (3 GI, 2 cost)	• Kidney (N=7), liver (N=7), heart (N=5) • Preexisting DM (N=16), PTDM (N=3) • Other outcomes: tacrolimus levels ↔ insulin dose ↓ in 57%, oral agents ↓ in 57%

				therapy Exclusion: • < 19 years • T1DM • GLP1RA therapy < 3 months • No follow-up • Nonadherence to GLP1RA				
Singh et al, 2020[51] (N=88)	Retrospective, single-center US	24	Dulaglutide (N=63) Liraglutide (N=25)	Inclusion • >18 years • SOT recipients with T2DM • Dulaglutide or liraglutide therapy for >6 months Exclusion: • h/o medullary or thyroid C-cell carcinoma, pancreatitis, multiple endocrine neoplasia syndrome type-2 or severe GI disease •	Dulaglutide vs. liraglutide eGFR • Median 47 ml/min/1.73 m^2 vs. 42.48 ml/min/1.73 m^2 HbA1c • Median 7.5% vs 7.5%	2140 days, 2933 days	Dulaglutide vs. liraglutide • HbA1c: Dulaglutide ≈ Liraglutide • eGFR: Dulaglutide > Liraglutide • Weight: Dulaglutide > Liraglutide • Hypoglycemia (6.3% vs 24%), no severe hypoglycemia, GI (0-3% vs 4-12%), cholelithiasis (0% vs 4%), no pancreatitis, gallstones or thyroid cancer, 1 PTLD in dulaglutide • Discontinuation: not reported	• Dulaglutide group reported in Singh 2019 • Dulaglutide: kidney 81%, liver 16%, liver-kidney 1.5%, heart 1.5%; Liraglutide: kidney 84%, liver 4%, liver-kidney 8%, heart 4% • Other outcomes: basal insulin dose ↓ (by 26% units/day in dulaglutide; 3.6% units/day in liraglutide)
Singh et al, 2019[50] (N=63)	Retrospective, single-center US	6 (N=59); 12 (N=49); 24 (N=13)	Dulaglutide (N=63)	Inclusion • >18 years • SOT recipients with T2DM • Dulaglutide therapy for >6 months Exclusion: • h/o medullary or thyroid C-cell carcinoma, pancreatitis, multiple endocrine neoplasia syndrome type-2 or severe GI disease	eGFR • 47.13 ml/min/1.73 m^2 (not specified) HbA1c • 7.59% (not specified)	Median 47.8 months (Range 7.8-330)	6-month follow-up (N=59) • HbA1c: ↓ • eGFR: ↔ • Weight: ↓ • Hypoglycemia (N=4), no severe hypoglycemia, nausea (N=2), vomiting (N=1), diarrhea (N=2), GI (1.5-3%), no pancreatitis, gallstones or thyroid cancer, PTLD (N=1), angina (N=1) • Discontinuation: not reported	• Dulaglutide: kidney 81%, liver 16%, liver-kidney 1.5%, heart 1.5% • Preexisting DM (N=43), PTDM (N=20) • Other outcomes: insulin dose ↓, 2 deaths (1 sepsis, 1 cardiac arrest)
Liou et al, 2018[57] (N=7)	Retrospective, single-center Taiwan	19.4±7.6 months (range 10.5-27.6)	Liraglutide (N=7)	Inclusion: KTR with liraglutide therapy Exclusion: N/A	eGFR • Mean 67.66±18.69 ml/min (range 38.29-92.59) HbA1c • Mean 10.04±1.61% (Range 8.1-12.1)	Not reported	• HbA1c: ↓ • eGFR: ↔ (best eGFR ↑) • Weight: ↔ (Nadir weight ↓) • No hypoglycemia, mild/temporary nausea, reduced appetite, HA, injection-site pain, and weakness • 2 discontinued (1 nausea/vomiting; 1	• Other outcome: tacrolimus dose reduced in 3/5 patients to maintain an optimal level.

							uncontrolled HA, dizziness, and rhinorrhea)	

Table 3 Abbreviations: Months (m), transplant (TXP), adverse events (AE), treatment (TXT), Type 2 diabetes mellitus (T2DM), glucagon-like peptide-1 receptor agonists (GLP1RA), United States (US), post-transplant diabetes mellitus (PTDM), Hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), interquartile range (IQR), heart failure (HF), myocardial infarction (MI), systolic blood pressure (SBP), low-density lipoprotein (LDL), triglyceride (TG), diabetes mellitus (DM), week (wk), not applicable (N/A), calcineurin inhibitors (CNI), gastrointestinal (GI), post-transplant lymphoproliferative disorder (PTLD), headache (HA)

SGLT2i Agents

Overview in General Population

SGLT2i agents block glucose reabsorption in the proximal tubule to induce glycosuria and thereby decreasing blood glucose through an insulin-independent mechanism.[60] These agents reduce HbA1c by 0.5-1% and carry a low risk for hypoglycemia.[61] In addition to the effects on glycemia, SGLT2i have shown to improve cardiovascular outcomes in patients with ASCVD and heart failure (HF) and be renoprotective in CKD patients (Table 1).[18,62–68] With labeled indications for T2DM, CKD, and now HF regardless of ventricular ejection fraction, SGLT2i have become attractive agents for many patient populations. These agents have also been shown to increase magnesium levels which could be beneficial to KTR with chronic hypomagnesemia and improving cardiovascular outcomes.[69,70] However, the support for their use in KTR remains unclear. The main concerns surrounding the use of this class of medications in KTR is increased risk of genitourinary infections in an already immunocompromised population and an initial increase in serum creatine noted in the general population (Table 2).[25]

Literature Summary in Kidney Transplant

Search terms resulted in 151 results, with eleven articles meeting review criteria on SGLT-2i use for the management of T2DM or PTDM in KTR. Prospective data on the use of SGLT2i in KTR include one placebo-controlled trial, two pilot studies, and one observational case series. The remaining seven articles are retrospective reviews (Table 4). The most commonly assessed SGLT2i was empagliflozin (n=9), followed by canagliflozin (n=5) and dapagliflozin (n=5), as well as one study also reporting use with luseogliflozin, ipragliflozin, and tofogliflozin. Of note, luseogliflozin, ipragliflozin and tofogliflozin

are not available in United States. The duration between transplant and the start of SGT2i varied between studies. The earliest reported use was at 3 months.[71] Two studies allowed the use of SGLT2i at 6 or 12 months post-transplant, however the average start times were much greater at 69 and 36 months respectively.[72,73] On average, the majority of the studies reported at least a 1-year duration between transplant and SGLT2i initiation. While the duration of follow-up ranged from 1 month to >5 years across all included studies, most patients were followed ≤1 year.

The majority of trials required stable renal function as an inclusion criterion with most reporting average baseline eGFRs ≥ 60 mL/min/1.73 m^2.[71–80] Similar to reported data in non-transplant patients, an initial increase in SCr was most commonly seen within the first 1-2 months after initiation and then recovered to have no significant difference thereafter.[72,73,76,78,80] In the study by Lim et al, 15.6% of the population noted > 10% decline in eGFR at 1 month ("dippers") that appeared to recover by month 5.[78] However, the authors note that there was no significant difference in the eGFR between dippers and non-dippers at any point in the study. Starting SGLT2i within 397 days and mean tacrolimus levels were identified as independent risk factors in the dipper group. In addition, SGLT2i users have a significantly lower doubling time for SCr compared to the non-users. As it relates to glycemic efficacy, Halden et al. reported that an eGFR ≥ 60 mL/min/1.73 m^2 had greater HbA1c reductions and was also the only study to find a significant increase in hemoglobin and hematocrit.[72] Three studies found increased serum magnesium levels and three studies reported decreased uric acid levels.[72–75] No studies showed a sustained significant difference in worsening renal function in KTR treated with SGLT2i.

Reported average baseline HbA1c at SGLT2i initiation varied from 6.5% to 9.3% (Table 4). Reductions in HbA1c varied between 0.1%-1.9% with the concomitant use of other antihyperglycemic agents. Several studies showed a significant decline in HbA1c when baseline HbA1c was > 8%.[71,72,77,79] As noted above, HbA1c reduction was greater with eGFR > 60 mL/min/1.73 m^2.[72] One strategy for

adjusting concomitant medications was to reduce the dose of insulin by 25% when initiating SGLT2i and titrate according to glucose control.[74] Monotherapy with empagliflozin 10 mg daily had worse glycemic outcomes necessitating the initiation of insulin in 50% of patients at 4 weeks and low persistence at 1 year (57% drop out) due to poor glycemic control.[73]

Impact on weight reduction was variable with the use of SGTL2i (Table 4). In those that reported significant decrease, the changes in weight varied from 0.7 kg to 2.95 kg.[71–73,75,77,81] Baseline renal function did not determine weight loss.[72] There were no studies that reported an increase in weight with SGLT2i use. Additionally, AlKiindi et al. reported a significant reduction in body mass index (BMI) from 32.7±7.2 kg/m^2 at baseline to 27.4±4.2 kg/m^2 at 12 months.[77] Based on review of the studies included in the table, a decrease in weight of ~1-2 kg is commonly seen after SGLT2i initiation with declines seen as early as 1-3 month that are maintained thereafter.

Consistent effects of SGLT2i use on blood pressure in KTR appear to be mixed. Most studies included found non-significant reductions in blood pressure. Of the two studies reporting significant blood pressure reductions, there was only one study to report a significant reduction in SBP of 8mmHg at 6 months and only one study that found a significant difference in diastolic pressures in those who had remained in the study at 12 months.[71,73] Of note, there were two studies that reported patients who had reductions in their antihypertensive medications.[72,74]

The most commonly reported adverse event after SGLT2i initiation was urinary tract infection (UTI). Those with a prior history of UTI were more likely to be affected. One study reported a patient with a history of recurrent UTI was hospitalized due to urosepsis while another study reported one patient hospitalized for diabetic ketoacidosis with a concurrent UTI.[72,79] Three studies had exclusion criteria for patients with a history of UTI and one study required unspecified prophylactic antibiotics

in patients with a UTI history.[71,74,75,77] Conversely, four studies reported no significant differences in increased UTI risk compared to non-SGLT2i groups.[72,73,78,81]

SGLT2i Summary

The majority of the studies reported at least a 1-year duration between transplant and SGLT2i initiation and most follow up periods were ≤1 year. The effects on HbA1c, eGFR, and weight with SGLT2i in KTR were comparable to that in the general patient population for the periods evaluated. Effects on blood pressure were inconsistent in SOT. This could be attributed to the concomitant use of CNI or corticosteroids; however, this was not specifically studied. These agents may also be beneficial by helping to increase magnesium levels and decrease uric acid levels. The most reported adverse effect was UTI. While rates appeared similar to that of the general population, SGLT2i should be used cautiously and only under close supervision in KTR with known risk factors or predisposing conditions for UTIs such as a history of recurrent UTIs, urinary retention, voiding dysfunction, urethral strictures, urinary obstruction, neurogenic bladder dysfunction, or catheterization which are often excluded in these studies.[82,83] There was no study evaluating effects on cardiovascular outcomes.

Table 4. Summary of SGLT2i Studies Included in Analysis

Study	Type, location	Follow up (m)	Treatment arm(s) (N)	Patient population	Baseline eGFR & HbA1c	Time from TXP	Results: HbA1c, eGFR, weight, AE, Discontinued txt	Comments
Rajasekeran et al.[80] 2017 N=10	Retrospective case series, Canada	80.5 person-months	Canagliflozin	Inclusion: • ≥ 18 years • KTR (N=6) or SPKTR (N=4)	eGFR • SPKTR Mean (SD) 60 (14) ml/min/1.73 m^2 • KTR Mean (SD) 78 (18.2) ml/min/1.73 m^2 HbA1c • SPKTR Mean (SD) 7.4 (1.1) % • KTR Mean (SD) 8.6 (1.4) %	SPKTR Mean (SD) 3.5 y (3.9) KTR Mean (SD) 4.4 y (3.3)	• HbA1c: ↓ • eGFR: ↔ • Weight: ↓ • AE: No urinary or mycotic infections, N=1 hypoglycemia, N=1 cellulitis • NR	• 80% NODAT • BP ↓ • Hematocrit ↔

Schwaiger et al. 2019[73] N=14	Prospective noninferiority pilot study, Austria	1m primary endpoint (N=14); 12m outcomes (N=8)	Empagliflozin 10 mg/day monotherapy • Insulin washout phase during first 3 days, insulin could be reinitiated after 4weeks primary end point • Any oral agents were also d/c	Inclusion: • ≥ 18 years • ≥6m post-txp • ≥6m of prior PTDM treatment • Receiving insulin but no <40 units/day short acting Exclusion: • eGFR<30 ml/min/1.73 m^2 • ≥40 units/day shorting acting insulin • HbA1c ≥8.5% • Pre-transplant DM	eGFR • Mean (SD) 55.6 (20.3) ml/min/1.73 m^2 HbA1c • Mean (SD) 6.5 (0.8) %	Mean (SD): 5.8 y (4.8)	• HbA1c: ↔ (4w), ↑(12m) • eGFR: ↓(4w), ↔ (12m) • Weight: ↓(4w), ↓(12m) • AE: N=3 & 5 UTI (4w&12m), N=1 uncomplicated balanitis • Discontinued txt: N=6 after 4w for glycemic control (N=2), eGFR (N=1), UTI (N=2), rejection (N=1), pneumonia requiring hospitalization (N=1)	• Primary end point: intra-individual difference in OGTT 2-hr glucose level between baseline and 4w: ↑ • 4w oral glucose insulin resistance ↑ and sensitivity ↓ • Baseline DM agents: long acting insulin (57%), short acting insulin (29%), combination insulin (43%), linagliptin (14%), sitagliptin (7%), metformin (7%) • 50% were reintroduced to insulin after 4w • DBP ↓ • Magnesium ↑ • Uric acid ↓ • Hemoglobin and hematocrit ↔
Halden et al. 2019[72] (N=49 randomized, 44 completed)	Prospective, Double blind, randomized controlled trial, Norway	6	Canagliflozin 10 mg/d (n=22): Placebo (n=22)	Inclusion: • ≥ 18 years • ≥1y post-txp • NODAT • <20% SCr deviation in last 2m • ≥3m stable immunosuppression Exclusion: • eGFR<30 ml/min/1.73 m^2 • Pregnant or nursing	eGFR • Median (IQR) 66 (57-68): 59 (52-72) ml/min/1.73 m^2 HbA1c • Median (IQR) 6.9 (6.5-8.2): 6.8 (6.1-7.2) %	Median (IQR) 3 y (1-16): 3 y (1-15)	• HbA1c: ↓ • eGFR: ↓ (2m), ↔ (6m) • Weight: ↓ • AE: Urosepsis 1:0 (hx of recurrent UTI), UTI 3:3, genital yeast infection 1:0, dizziness 2:0, hematuria 1:0 • Discontinued txt: N=2 (recurrent UTI, urosepsis): 3 (withdrew consent, colon cancer, no longer fulfilling PTDM criteria)	• Concomitant DM agents: DDP4i (36%:50%), Metformin (4.6%:4.6%), SU (14%:18%), Insulin (23%:14%), None (32%:32%) • Baseline HbA1c >8% had ↑ HbA1c reduction • eGFR ≥60 had ↑ HbA1c reduction • BP ↔, n=2 had ↓ dose of BP meds • Magnesium ↑ • Uric acid ↓ • Hemoglobin and hematocrit ↑
Shah, et al. 2019[71] (N=25)	Prospective pilot study, India	6	Canagliflozin 100 mg/d	Inclusion: • ≥ 18 years • CrCl >60 mL/min • HbA1c >6.5% Exclusion: • CrCl <60 mL/min • Alanine aminotransferase >2x upper limit of normal • Total bilirubin >1.5 mg/dL • Recent UTI or genital mycotic infection	CrCl • Mean (SD) 86 (20) ml/min/1.73 m^2 HbA1c • Mean (SD) 8.5 (1.5) %	Mean 2.7 y Range: 3 m -13 y	• HbA1c: ↓ • eGFR: ↔ • Weight: ↓ • AE: Fatigue n=3, improved with increased water intake • Discontinued txt: N=1 self-discontinued after 2 weeks due to non-significant rise in SCr	• Did not titrate to 300 mg dose • 20% NODAT • Baseline tacrolimus level 6.7 ± 3.7 and 6.1 ± 2 ng/ml at 6m • N=20 T2DM prior to transplant • Concomitant DM agents: (n=NR): sulfonylurea, metformin, DPP4, α-glucosidase inhibitor, and/or insulin • Doses were reduced when starting • BP↓
Mahling et al.2019[74] (N=10)	Prospective observational, case series, Germany	Median (IQR): 12 (5.2-12.0)	Empagliflozin (started prior to study inclusion-dose not specified) • ↓ insulin 25% at start then	Inclusion: • eGFR ≥45 ml/min/1.73 m^2 Exclusion: • T1DM • History recurrent UTI	eGFR • Median (IQR) 57 (47-73) ml/min/1.73 m^2 HbA1c • Median (IQR) 7.3% (6.4-7.8)	Median (IQR): 5.9 y (4.4-8.8)	• HbA1c: ↔ • eGFR: ↔ • Weight: ↓ • AE: UTI N=2, AKI N=1 , small DM ulcer treated successfully with local txt N=1	• 40% NODAT • Concomitant DM agents: insulin 50%, metformin 20%, DPP4i 20% • Insulin ↓ 10-25% • SBP ↓ • Uric acid ↓

			titrated PRN • If on, diuretic or BP medications were reduced or paused by treating physician				• Discontinued txt: N=2 self-discontinued (1 fatigue, 1 respiratory tract infection and temporary decline in renal function)	• Hematocrit ↑
Attallah & Yassine 2019[76] (N=8)	Retrospective. case series, United Arab Emirates	12	Empagliflozin 25mg/day	Inclusion: • PTDM	eGFR • Mean 78.2 (NR) ml/min/1.73 m^2 HbA1c • Mean (range) 8.1 (7.8-8.5) %	Mean (range) 21m (11-31)	• HbA1c: ↓ 3m, then ↔ • eGFR: ↓ 1m, then ↔ • Weight: ↓ 3m, then ↔ • AE: N=2 nausea , N=3 UTIs (1 person x 2) • Discontinued txt: N=1 d/c at 10m due to recurrent UTI	• Concomitant DM agents: metformin (N=8), DPP4i (N=2), insulin (N=0) • All on ACEi or ARB • NODAT (N=4) • UP/CR ↓
AlKindi et al. 2020[77] (N=8)	Retrospective case series, United Arab Emirates	Range: 3m-2y	Empagliflozin N=6 (10mg, n=5; 25mg, n=1) Dapagliflozin 25mg N=2	Inclusion • Diabetic renal transplant recipients • Started on SGLT2 between 06/2016-01/2019	eGFR • Mean (SD) 75.8 (13.4) ml/min/1.73 m^2 HbA1c • Mean (SD) 9.3% (1.4)	Mean (SD) 9.6y (6.41)	• HbA1c: ↓ • eGFR: ↔ • Weight: ↓ • AE: UTI requiring hospitalization (N=1) • Discontinued txt: NR	• NODAT (N=6) • Concomitant DM agents: metformin (37.5%), SU (62.5%), DPP4i (37.5%), insulin (37.5%), GLP1RA (37.5%) • N=2 patients with history of UTI were on abx ppx
Song et al.2020[75] (n=50)	Retrospective chart review, US	Mean: 101 days	Empagliflozin (N=43) Canagliflozin (N=6) Dapagliflozin (N=1)	Inclusion • PTDM • eGFR ≥30 Exclusion • AKI in prior ≤30d • UTI in prior 6m	eGFR • Mean (SD) 66.7 ml/min/1.73 m^2 ○ (14% 30-45 ml/min/1.73 m^2) HbA1c • Mean (SD) 7.1% (0.1)	Median (IQR) 319.5d (122-696) • 40% within 200d	• HbA1c: ↔ • eGFR: ↔ • Weight: ↓ • AE: UTI (N=7) • Discontinued txt: N=9 (5, UTI; 1 genital yeast infection, 1 native disease recurrence, 1 PTDM resolution, 1 physician preference)	• Concomitant DM agents: metformin (64%), SU (2%), DPP4i (24%), insulin (84%), GLP1RA (10%) • Magnesium ↑
Hisadome, et al.2021[81] (N=89)	Retrospective, observational, study, Japan	48 weeks	SGLT2 (N=29) Canagliflozin (N=9)Empagliflozin (N=4) Dapagliflozin (N=3) Luseogliflozin (N=5} Ipragliflozin (N=7)Tofogliflozin n=1) Vs Other oral glycemic agent (N=60) DDP4i (N=42) meglitinides (N=9) metformin (N=4) SU (N=4) α-glucosidase	Inclusion • ESRD patients with T2DM nephropathy prior to transplant • Newly administered oral anti-hyperglycemic agents after transplant Exclusion • Follow up at outside institutions • <1y f/u • Missing data on variates requiring analysis	eGFR • Mean (SD) 50.4 (13.9) ml/min/1.73 m^2: 47.5 (13.1) ml/min/1.73 m^2 HbA1c • Mean (SD) 7.7% (0.9) : 7.6% (1.1)	Not reported	• HbA1c: ↔ • eGFR: ↔ • Weight: ↓ • AE: UTI (2:0), cardiovascular disease (0:2), BPAR (1:1) • Discontinued txt: NR	• BP ↔ • N=85 after matched probability of treatment weight

			inh (N=1)					
Lim et al. 2022[78] (n=2083)	Multicenter retrospective cohort study, South Korea	Mean (SD) 62.9m (42.2)	Empagliflozin (n=150) Dapagliflozin (n=76) (doses not specified) VS Non-SGLT2i users (n=1857)	Inclusion • Either pre-existing DM or NODAT Exclusion • Pancreas transplant • Prescribed SGLT2i <90 from transplant	eGFR at 3m post-txp • Mean (SD) 66.9 (17.7) ml/min/1.73 m^2: 68.4 (20.1) ml/min/1.73 m^2 HbA1c at 3m post-txp • Mean (SD) 7.3% (1.4): 7.3 (1.4)	Mean (SD) 3.8y (4.5)	• HbA1c: NR • eGFR: ↑ • Weight: NR • AE: Similar incidence of bacterial and fungal UTIs between groups • Discontinued txt: NR	• Composite primary outcome of all cause mortality or death censored graft failure or SCr doubling was significantly lower in the SGLT2 group • 74% pre-txp DM • While overall, eGFR remained stable among all SGLT2i users, 15.6% were classified as "dippers" that had >10% eGFR decline over the first month • Use <397 days after KT and mean tac trough level >7.5ng/mL were independent risk factors for eGFR dip of ≥10% • Concomitant DM agents: metformin (88%:55%), SU (46%:34%), DPP4i (52%:55%), insulin (62%:55%) • UP/CR: no difference
Lemke et al. 2022[79] (n=39)	Single health system, retrospective, descriptive study, US	12m	Canagliflozin (N=12) Dapagliflozin (N=3) Empagliflozin (N=24)	Inclusion • NODAT or pre-transplant DM • SGLT2 prescribed from 4/2013 – 10/2020 • Care managed solely within study health system	eGFR • Median (IQR) 69 (54-76) ml/min/1.73 m^2 HbA1c • Median (IQR) 8.4% (7.8-9.2)	Median (IQR): 28m (16-60)	• HbA1c: ↓ • eGFR: ↔ • Weight: ↓ (n=15, 3m) • AE: N=6 UTI (3 requiring hospitalizations, 1 ICU), n=1 DKA requiring hospitalization and concurrent UTI, n=2 diabetic foot ulcers (1 with ulcer at start of initiation, the other after years of being on SGLT2 and progressed to amputation), n=2 mild hypoglycemia, n=1 AKI 90d after initiation • Discontinued txt: 17 d/c after a median (IQR) 244d (117-401), n=6 for cost, n=4 declining eGFR, n=3 for infectious complications, n=1 poor wound healing, n=1 hypoglycemia, n=1 self d/c, n=1 death unrelated to SGLT2i	• PTDM (N=17) • Remained on therapy ≥1yr (N=27) • Liver/kidney (N=1) kidney/pancreas (N=1) • 70% also on insulin • 5/6 patients with UTI had a hx of UTIs • Hemoglobin and hematocrit ↔

Table 4 Abbreviations: Months (m), transplant (TXP), adverse events (AE), treatment (TXT), glomerular filtration rate (eGFR), adverse effect (AE), Type 2 diabetes mellitus (T2DM), new onset diabetes after transplant (NODAT), interquartile range (IQR), sodium glucose co-transporter 2 inhibitors (SGLT2i), kidney transplant recipient (KTR), simultaneously pancreas/kidney transplant recipient (SPKTR), Hemoglobin A1c (HbA1c), diabetes mellitus (DM), urinary tract infection (UTI), oral glucose tolerance test (OGTT), diastolic blood pressure (DBP), systolic blood pressure (SBP), serum creatinine

(SCr), blood pressure (BP), acute kidney injury (AKI), NR (not reported), urine protein: creatine ratio (UP/CR), antibiotic prophylaxis (abx ppx), United States (US), standard deviation (SD), biopsy proven acute rejection (BPAR), diabetic ketoacidosis (DKA), discontinue (d/c)

DPP4i Agents

Overview in General Population

DPP4i agents work to inhibit degradation of incretins, resulting in increased levels of the incretins glucagon-like peptide-1 and glucose dependent insulinotropic peptide. Linagliptin, sitagliptin, saxagliptin, and alogliptin are FDA approved as adjunctive therapy or monotherapy for treatment of T2DM. Gemigliptin and vildagliptin are not currently available in the United States, however, are utilized for T2DM in various countries. Although sitagliptin, saxagliptin, and alogliptin require renal dose adjustments, linagliptin may be used in renal impairment without dose adjustment. Due to lack of additive antihyperglycemic benefits, combination use of DPP4i with a GLP1RA is typically avoided.[17] (Table 2)

According to the ADA, DPP4i are typically recommended in addition to metformin in patients without established ASCVD or CKD and a compelling need to minimize hypoglycemia in the general population.[17] DPP4i have intermediate efficacy with lowering HbA1c with reductions of approximately 0.5% to 1%. Given its minimal impact on weight, DPP4i may also be used as add on therapy to SGLT2i agents in patients with a compelling need to minimize weight gain or promote weight loss with HbA1c results that remain above target (Table 1). DPP4i have not shown any renal protective effects in the general population with no significant changes to eGFR or serum creatinine in the SAVOR-TIMI study.[84]

GI effects are the most common side effects of DPP4i, including nausea, vomiting, and diarrhea. Given pancreatitis has been reported with DPP4i, caution has been taken to avoid DPP4i in patients

with pancreatitis or at risk of pancreatitis.[85] Hypoglycemia risk with DPP4i use has remained low. An increased risk of HF hospitalization in patients with cardiovascular disease has been observed with use of saxagliptin and alogliptin, limiting its use in patients with HF. The EXAMINE study compared alogliptin to placebo and showed an overall higher incidence of HF hospitalization in patients with HF who received alogliptin (2.2% vs. 1.3%) that was statistically significant.[86] A meta-analysis of DPP4i use found that all DPP4i (excluding saxagliptin) were not associated with an increased risk of HF (OR: 1.05; 95% CI: 0.96-1.15).[87] As a result, guideline recommendations state DPP4i (excluding saxagliptin) may be utilized as add on therapy in patients with HF; however, other agents are preferred.[17]

Literature Summary in Kidney Transplant

Search terms resulted in 62 results, with 15 articles meeting review criteria on the use of DPP4i in kidney transplant for the management of T2DM or PTDM (Table 5). Fourteen studies solely evaluated KTR and one study evaluated both kidney and liver transplant recipients. Eleven studies were retrospective evaluations and 5 studies were prospective (4 randomized controlled trials,1 prospective single center pilot study). Linagliptin was the most commonly assessed DPP4i with 5 studies evaluating its use, followed by 4 studies evaluating sitaglipin as the sole DPP4i. Only three studies evaluated a small portion of patients on DPP4i monotherapy, demonstrating a decrease in HbA1c with no significant changes in weight.[88–90] One study evaluated sitagliptin monotherapy, however, majority of patients required other diabetes medications for glucose control at end of follow-up analysis.[91] All other studies evaluated DPP4i in combination with other glycemic agents. Baseline eGFR was lower in studies evaluating linagliptin given no renal adjustments are necessary for its use. Majority of studies evaluating any DPP4i had an average baseline eGFR ≥60 mL/min/1.73m^2. There was wide variability in the mean/median time from transplant to DPP4i initiation in the 9 studies that reported it (Table 5). The earliest start to DPP4i initiation was <24 hours after kidney transplant, with most studies evaluating use >1 year post-transplant. The duration

of follow up ranged from 2 months to 24 months. Baseline HbA1c values that were reported in 12 studies ranged from approximately 5% to 9%.

Of the 14 studies that reported HbA1c, 11 studies reported a decrease in HbA1c with use of a DPP4i, ranging from 0.1% to 1.4%. However, only three studies reported a decrease in HbA1c with DPP4i monotherapy, with only one study demonstrating a statistically significant decrease.[89,90,92] Although 24 patients received DPP4i monotherapy in this study, 71 patients received other glycemic agents with a decrease in HbA1c of 1.4% (P<0.0001) for the entire cohort.[92] Changes in weight were not reported in 6 of the 15 studies. Eight studies reported no change in weight with one of these studies demonstrating a non-significant increase in weight. Only one study observed a minimal decrease in weight of approximately 0.4 kg.[93] Eleven studies showed DPP4i use had no impact on eGFR, with 1 study demonstrating a mean increase in eGFR of 15.77 mL/min/1.73 m^2 (P<0.0001). Change in eGFR was not evaluated in 3 studies. The most common adverse effects reported including elevated liver enzymes, pancreatitis, UTI, GI effects and headache with sinusitis. No side effects with DPP4i use were reported in 3 studies. Although minimal hypoglycemia was reported in 7 studies, majority of these patients were also receiving either insulin therapy or other glycemic agents. Of the eleven studies reporting discontinuation of DPP4i, 8 studies demonstrated no discontinuation of DPP4i therapy. The most common reason for discontinuation was hyperglycemia.

Adjustment of concomitant glycemic medications was discussed in 3 studies.[91,94,95] One retrospective, single center study based in Mexico evaluated linagliptin 5mg daily with a starting dose of basal bolus insulin regimen of approximately 0.5 unit/kg/day and adjusted according to international guidelines.[94] A single center in Australia managed uncontrolled blood glucose on linagliptin therapy with either a sulfonylurea or metformin, depending on renal function.[95] Additional insulin therapy was utilized if blood glucose remained out of target range. Lastly, a single center in the US utilized sitagliptin as the initial treatment alone of PTDM with discontinuation of

other glycemic agents. However, majority of patients required additional glycemic agents for blood glucose control at end of follow-up analysis.[91] One study reported an increase in cyclosporine levels with sitagliptin therapy.[98] However, majority of studies demonstrated no changes in calcineurin trough levels with DPP4i therapy.[88,89,91,97,100-102]

DPP4i Summary

Although majority of the literature evaluating DPP4i use in KTR is limited to retrospective studies, current evidence demonstrates DPP4i may help reduce HbA1c in this patient population in combination with other antihyperglycemic agents with minimal adverse effects and discontinuation. Majority of studies observed stable calcineurin inhibitor trough levels with DPP4i therapy.

Table 5. Summary of DPP4i Studies Included in Analysis

Study	Type, location	Follow up (m)	Treatment arm(s) (n)	Patient population	Baseline eGFR & HbA1c	Time from TXP	Results: HbA1c, eGFR, w Discontinued txt
Mpratsiakou et al, 2021[96] (N=17)	Retrospective, single center Greece	12	DPP4i (N=12) Insulin monotherapy (N=5)	Inclusion • >18 years • History of kidney transplant • NODAT diagnosis • No history of previous antidiabetic treatment Exclusion: • Diabetes prior to transplant • Loss of follow-up by 12 months	eGFR • Mean (SD): 58.83±16.9 ml/min/1.73 m^2:Not reported HbA1c • Mean (SD): 6.6±0.7%: Not reported	Not reported	• HbA1c: ↓ • eGFR: ↔ (pre- and • Weight: ↔ (pre- a • AE: No side effects DPP4i • Discontinuation: (N
Sanyal et al, 2021[92] (N=95)	Retrospective, cross-sectional India	12	Linagliptin (N=95)	Inclusion • ≥ 18 years • Living kidney transplant • NODAT diagnosis with 1 year follow-up after endocrinology referral Exclusion: • Transient post-transplant hyperglycemia	eGFR • Mean (SD): 53.95±16.1 ml/min/1.73 m^2 HbA1c • Mean (SD): 8.48±1.08%	Not reported	• HbA1c: ↓ • eGFR: ↓ • Weight: ↑ (NS) • AE: No hypoglycem monotherapy, 15 p hypoglycemia on li insulin • Discontinuation: N
Attallah et al, 2021[88] (N=42)	Retrospective, single center Abu Dhabi	12	Linagliptin (N=42)	Inclusion • KTR receiving linagliptin • 12 mo follow-up Exclusion: • Receiving other DPP4i • < 3 mo after KT	Serum creatinine • Mean: 1.5±0.3 ml/min/1.73 m^2 HbA1c • Mean: 8.2%	Mean: 25 months	• HbA1c: ↓ • eGFR: ↔ • Weight: ↔ • AE: N/V (N=4), MI (CMV (N=1), No hyp • Discontinuation: (N
Guardado-	Retrospectiv	6, 12	Linagliptin + Insulin	Inclusion	Serum creatinine (1 mo	<24h	• HbA1c: ↔

Mendoza, et al, 2019[94] (N=28)	e, single center Mexico		(N=14) Insulin monotherapy (N=14)	• KT with hyperglycemia (>140 mg/dL) <24h after KT	post-KT) • Mean (SD): 1.7±0.2: 1.7±0.3 ml/min/1.73 m^2 HbA1c • Mean (SD): 7.15±1.46 : 8.05±1.39%		• eGFR: ↔ • Weight: Not report • AE: Hypoglycemia: hypoglycemia wors monotherapy • Discontinuation: N
Thiruveng adam et al, 2019[95] (N=147)	Retrospectiv e, single center Australia	Time to OGTT	Linagliptin (N=41) Historical cohort conventional therapy (N=106)	Inclusion • FBG >126 mg/DL or random BG >200 mg/dL at least 48 h post-KT transplant • OGTT at 3 months post-transplant Exclusion: • OGTT not performed within 1 year of transplant • No clinic letters or details on history of diabetes, development of PTDM or medication lists	Serum creatinine • Not reported HbA1c • Not reported	48h post-transplant	• HbA1c: Not reporte • eGFR: Not reported • Weight: Not report • AE: Not reported • Discontinuation: N
Bae et al, 2019[97] (N=84)	Retrospectiv e, single center South Korea	6	Gemigliptin (N=84)	Inclusion • Age > 20 years • KT or LT prescribed gemigliptin for >180 days Exclusion: • Graft failure • Immunosuppression discontinued for any reason	eGFR • Mean (SD): 57.59±20.81 ml/min/1.73 m^2 HbA1c • Mean (SD): 8.16±1.69%	Mean (SD): 7.21±7.32 years	• HbA1c: ↓ • eGFR: ↔ • Weight: Not report • AE: No adverse eff • Discontinuation: (N
Bae et al, 2016[98] (N=65)	Retrospectiv e, observation al study South Korea	3	DPP4i (N=65) • Vildagliptin (N=17) • Sitagliptin (N=28) • Linagliptin (N=20)	Inclusion • Diabetes mellitus and/or receiving antidiabetic medications at 1 year after KT • Initiated on DPP4i after transplant	eGFR • Mean (SD): 60.68±13.19 ml/min/1.73 m^2, 69.32±17.85 ml/min/1.73 m^2, 66.08±25.65 ml/min/1.73 m^2 HbA1c • Mean (SD): 7.57±2.11%, 7.76±1.21%, 8.11±1.29%	Mean (SD): 1.82±3, 1.86±3.31, 3.7±4.24 years	• HbA1c: ↓ • eGFR: ↔ • Weight: Not report • AE: Not reported • Discontinuation: N
Haidinger et al, 2015[99] (N=71)	Retrospectiv e, observation al, single center Austria	24	DPP4i (N=24) Any diabetic agent (N=47)	Inclusion • >6 mo after KT • Newly diagnosed PTDM Exclusion: • <6 mo after KT • Any antidiabetic treatment at baseline OGTT • History of pre-existing Type 1 or 2 DM	• Not reported	Not reported	• HbA1c: ↓ • eGFR: Not reporte • Weight: Not report • AE: UTI (N=3), Cou pneumonia (N=2), enzymes (N=3), hy (N=1), pancreatitis • Discontinuation: (N
Haidinger et al,	Randomized , double-	4	Vildagliptin (N=16) Placebo (N=16)	Inclusion • ≥ 6 months after KT	eGFR • Mean (SD): 58.3±16.3	Mean (SD): 69.9±63.9	• HbA1c: ↓

2014[100] (N=32)	blind, placebo controlled Austria			• Newly diagnosed NODAT • Stable graft function Exclusion: • Prior history of Type 1 or 2 DM • Pregnancy • eGFR ≤ 30 ml/min/1.73 m^2 • Severe liver impairment	ml/min/1.73 m^2: 53.6±14.4 ml/min/1.73 m^2 HbA1c • Mean (SD): 6.7±0.73%: 6.7±0.82%	months: 51.4±47.2 months	• eGFR: ↔ • Weight: ↔ • AE: Elevated liver e pancreatitis 0:1, U pectoralis 1:0 • Discontinuation: d
Strom Halden et al, 2014[90] (N=19)	Randomized controlled cross-over Norway	2	Sitaglipin x 4 weeks, followed by 4 weeks sitaglipin-free period (or vice-versa) (N=19)	Inclusion • KT >1 year • Stable renal function • NODAT diagnosis • Stable prednisolone dose for last 3 months Exclusion: • Severe liver disease • eGFR<25 ml/min/1.73 m^2	eGFR • Median (IQR): 61 (43-85) ml/min/1.73 m^2 HbA1c • Median (IQR): 6.9 (6.7 - 7.3) %	Median (IQR): 1 (1-3)	• HbA1c: ↔ • eGFR: ↔ • Weight: ↔ • AE: Night sweats (N asymptomatic moc hypoglycemia (N=2 • Discontinuation: d sweats (N=1)
Boerner et al, 2014[91] (N=22)	Retrospectiv e, single center US	12	Sitaglipin (N=22)	Inclusion • KT with NODAT diagnosis Exclusion: • Diabetes prior to transplant • Death • Loss of follow-up prior to 12 months	eGFR • Not reported HbA1c • Not reported	Not reported	• HbA1c: ↓ • eGFR: ↔ • Weight: ↔ • AE: No effect on liv transaminases • Discontinuation: d hyperglycemia (N= discontinuation du (N=1)
Sanyal et al, 2013[89] (N=21)	Retrospectiv e, single center India	6	Linagliptin monotherapy (N=21)	Inclusion • KT with stable renal function • No past history of diabetes • Evaluated for NODAT (OGTT>200mg/dL)	eGFR • Mean (SD): 62.9±0.4 ml/min/1.73 m^2 HbA1c • Mean (SD): 8.2±0.78%	Not reported	• HbA1c: ↓ • eGFR: ↔ • Weight: ↔ • AE: Hypoglycemia with sinusitis (N=1 • Discontinuation: d
Werzowa et al, 2013[101] (N=48)	Randomized , placebo controlled Austria	3	Vildagliptin (N=16) Pioglitazone (N=16) Placebo (N=16)	Inclusion • ≥ 6 months after KT • Newly diagnosed NODAT • Stable graft function Exclusion: • Prior history of Type 1 or 2 DM • Pregnancy • eGFR ≤ 15 ml/min/1.73 m^2or need for dialysis • Severe liver impairment	eGFR • Mean (SD): 52.9±12 ml/min/1.73 m^2: 47.5±14.5 ml/min/1.73 m^2: 48.9±10 ml/min/1.73 m^2 (P=0.37) HbA1c • Mean (SD): 5.7±0.3%: 6.2±0.6%: 5.9±0.4% (P=0.01)	• Mean (SD): 75±71 months: 77±66 months: 59±49 months	• HbA1c: ↓ • eGFR: ↔ • Weight: ↔ • AE: Hypoglycemia with sinusitis (N=1 • Discontinuation: d
Soliman et al, 2013[93] (N=45)	Randomized controlled trial Egypt	3	Metformin + sitigliptin (N=28) Metformin + insulin glargine (N=17)	Inclusion • ≥ 6 months after KT • Newly diagnosed NODAT • Stable graft function Exclusion: • Prior history of Type 1 or 2 DM • BMI>40 kg/m^2 • Pregnancy • eGFR ≤ 30 ml/min/1.73 m^2 • Severe liver impairment • Severe blood glucose elevation (HbA1c >8.5%)	eGFR • Not reported HbA1c • Mean (SD): 7.7±0.9%: 7.5±0.7%	Median (IQR): 14.3 (6.8-8.6) months	• HbA1c: ↔ • eGFR: Not reporte • Weight: ↓ • AE: Hypoglycemia gastrointestinal 2:2 • Discontinuation: d
Lane et al, 2011[102] (N=15)	Prospective, single center pilot study US	3	Sitagliptin (N=15)	Inclusion • KT eGFR >30 ml/min/1.73 m^2 • Free of other chronic illnesses • HbA1c of 6.5% – 10%	eGFR • 58.9±4.4 ml/min/1.73 m^2 HbA1c • Mean (SD): 7.2±0.1%	Mean (SD): 4.7±1.0 years	• HbA1c: ↓ • eGFR: ↔ • Weight: Not report • AE: Mild abdomina loose stools, nause

							• hypoglycemia • Discontinuation: d

Table 5 abbreviations: months (m), transplant (TXP), adverse events (AE), treatment (TXT), Type 2 diabetes mellitus (T2DM), new onset diabetes after transplant (NODAT), interquartile range (IQR), dipeptidyl peptidase IV inhibitors (DPP4i), kidney transplant recipient (KTR), standard deviation (SD), glomerular filtration rate (eGFR), adverse effect (AE), not significant (NS), kidney transplant (KT), myocardial infarction (MI), urinary tract infection (UTI), oral glucose tolerance test (OGTT), fasting blood glucose (FBG), liver transplant (LT), body mass index (BMI), post-transplant diabetes mellitus (PTDM),), serum creatinine (SCr), not reported (NR), United States (US)

CLINICAL QUESTIONS/CLINICAL GUIDANCE FOR USE

Upon review of the literature, the following clinical questions were addressed to assist with guidance of practice along with a summary algorithm (Figure 1)

Which agents provide the greatest glycemic control and metabolic risk reduction in KTRs with T2DM/PTDM?

GLP1RA:

GLP1RA (dulaglutide, liraglutide, semaglutide), in combination with other antihyperglycemic agents, reduces HbA1c in stable KTRs with T2DM/PTDM (2C).

GLP1RA (dulaglutide, liraglutide, semaglutide) as monotherapy may reduce HbA1c in stable KTRs with T2DM/PTDM, although data are limited to non-transplant population (2D).

GLP1RA (dulaglutide, liraglutide, semaglutide) can reduce weight in stable, obese KTRs with T2DM/PTDM (2B).

SGLT2i:

SGLT2i (canaglifozin, dapaglifozin, empaglifozin), in combination with other antihyperglycemic agents, reduces HbA1c in stable kidney transplant (1B). Most significant benefit seen when HbA1c > 8% prior to SGLT2i initiation.

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) monotherapy is unlikely to significantly reduce HbA1c in stable KTRs with T2DM/PTDM (2C).

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) may reduce weight in stable KTRs, however results are variable and with no reports of weight gain (2D).

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) may reduce blood pressure in stable KTRs, however results are variable and modest (2D).

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) may increase serum magnesium concentrations, potentially minimizing the hypomagnesemia that is frequently experienced after kidney transplantation (2D).

blood pressure in stable KTRs, however results are variable and modest (2D).

DDP4i:

DPP4i (alogliptin, linagliptin, saxagliptin, sitagliptin), in combination with other antidiabetic agents, moderately reduces HbA1c in stable KTRs with T2DM/PTDM (1B).

DPP4i (alogliptin, linagliptin, saxagliptin, sitagliptin) monotherapy mildly reduces HbA1c in stable KTRs with T2DM/PTDM (2C).

Which agents provide the greatest cardiovascular and renal benefits in KTRs with T2DM/PTDM?

GLP1RA:

GLP1RA (dulaglutide, liraglutide, semaglutide) use in KTRs with T2DM/PTDM and established CVD may reduce major adverse cardiovascular outcomes, however cardiovascular outcomes were not directly studied in this population (2D).

GLP1RA (dulaglutide, liraglutide, semaglutide) use in KTRs with T2DM/PTDM and moderate CKD may reduce the incidence of new-onset or persistent macroalbuminuria, however data in this population are limited (2D).

SGLT2i:

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) use in KTRs with T2DM/PTDM and established CVD or HF may reduce major adverse cardiovascular outcomes, however cardiovascular outcomes were not directly studied in this population (2D).

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) use in KTRs with T2DM/PTDM may reduce progression of chronic kidney disease, however data in this population are limited (2D).

DPP4i:

Long-term cardiovascular or renal protective benefits have not been demonstrated with DPP4i use (2D).

What is ideal timeline to start specific agents post-transplant balancing risks and benefits in KTRs with T2DM/PTDM?

GLP1RA:

GLP1RA (dulaglutide, liraglutide, semaglutide) can be initiated at least 1-year post-transplant in stable KTRs with T2DM/PTDM (2B). GLP1RA use can be considered in the first post-transplant year, however data supporting initiation during this timeframe are limited (2C).

GLP1RA (dulaglutide, liraglutide, semaglutide) use should be reserved for stable KTRs with eGFR ≥ 45 mL/min/1.73 m^2 (2B). GLP1RA use in the setting of renal dysfunction (eGFR < 45 mL/min/1.73 m^2) post-kidney transplant is limited, however experience from non-transplant populations suggest use is safe with renal impairment (2D).

SGLT2i:

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) can be initiated at least 1-year post-transplant in stable KTRs with T2DM/PTDM (2B). SGLT2i use has been reported as early as 3 months post-transplant and can be considered in the first post-transplant year (2C).

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) use should be reserved for stable KTRs with eGFR ≥ 60 mL/min/1.73 m^2 (2B).

SGLT2i (canaglifozin, dapaglifozin, empaglifozin) use should be avoided in KTRs with a significant history of urinary tract infections (2C).

DPP4i:

DPP4i (alogliptin, linagliptin, saxagliptin, sitagliptin) can be initiated at least 1-year post-transplant in stable KTRs with T2DM/PTDM (2B). DPP4i use has been reported as early as 24-hours post-transplant and can be considered in the first post-transplant year

Alogliptin, saxagliptin, and sitagliptin use should be reserved for stable KTRs with eGFR ≥ 30 mL/min/1.73 m^2 (2B).

What monitoring parameters should be followed in the renal transplant population for novel antihyperglycemic agents?

In additional to the routine HbA1c recommendations for monitoring by ADA, the following monitoring parameters are suggested for the following drug categories:

GLP1RA:

KTRs using GLP1RA should be closely monitored for gastrointestinal adverse drug effects (e.g., nausea, vomiting, and diarrhea), pancreatitis, and injection site pain (1A).

SGLT2i:

Renal function should be assessed monthly for monthly x 3 followed by every 3 months, at minimum, in KTRs using SGLT2i, with dose adjustment or drug discontinuation as needed for renal insufficiency (1A).

Note: Comparable to reported data in non-transplant patients, an increase in SCr is commonly seen within the first 1-2 months after initiation that self-resolves

KTRs using SGLT2i should be routinely monitored for volume status and other factors predisposing risk for diabetic ketoacidosis (1A).

KTRs using SGLT2i should be closely monitoring for signs and symptoms of genitourinary infections.

Long-term safety data on the effects of prolonged glycosuria are lacking (1A).

DPP4i:

KTRs using DPP4i should be closely monitored for pancreatitis and elevated liver enzymes (1A).

How should concomitant antihyperglycemic agents be modified with the addition of novel antihyperglycemic agents?

GLP1RA:

Insulin dose requirements and need for other antihyperglycemic agents may be reduced in the setting of GLP1RA use. There is insufficient data to support empiric adjustments (2B).

SGLT2i:

Insulin dose requirements and need for other antihyperglycemic agents may be reduced in the setting of SGLT2i use. There is insufficient data to support empiric adjustments (2C).

DPP4i:

No empiric modifications to concomitant anti-hyperglycemic agents are recommended with the initiation of DPP4i (2B).

How should immunosuppressive therapies be modified with the addition of novel antihyperglycemic agents?

GLP1RA:

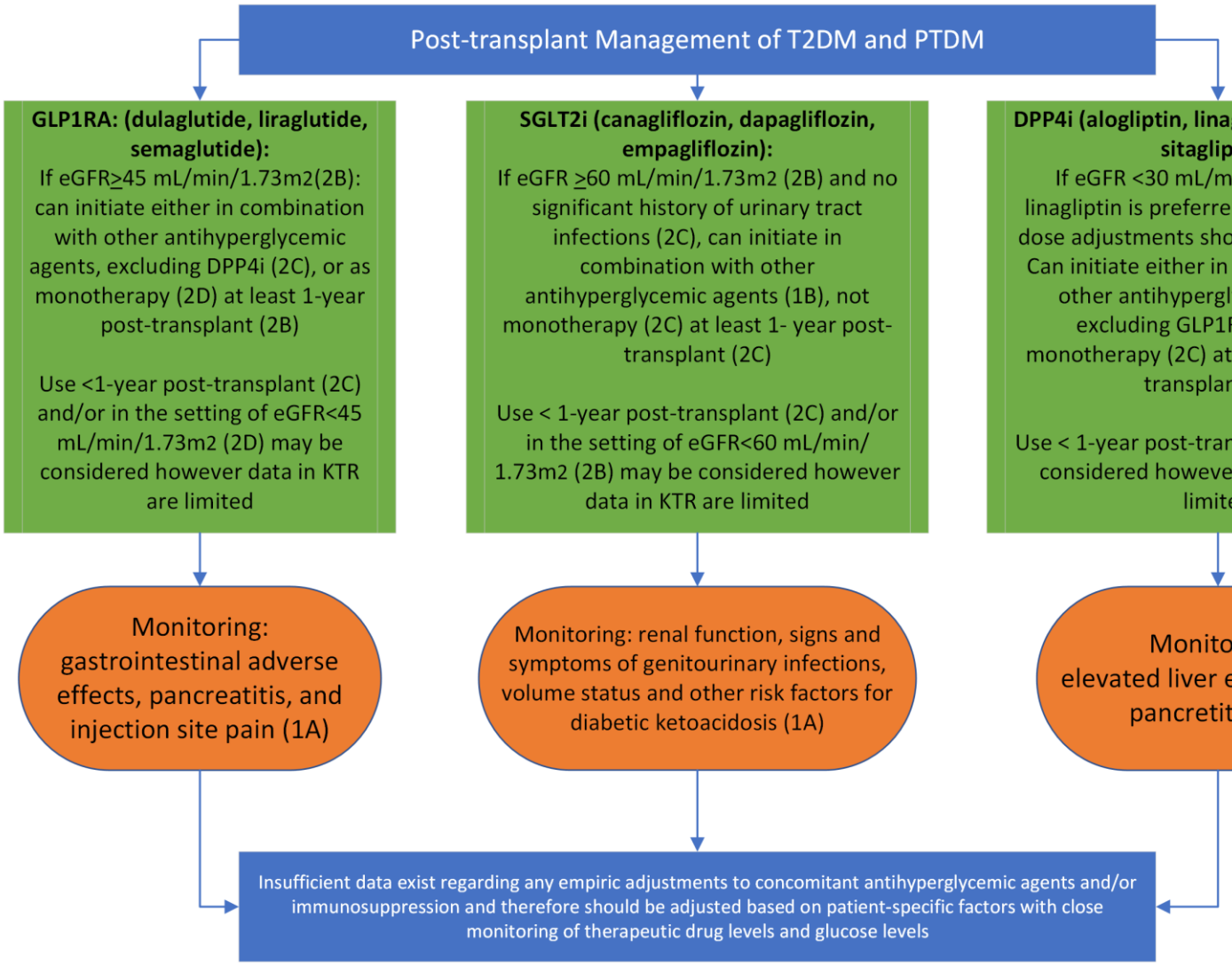
Empiric adjustments to transplant immunosuppression with initiation of GLP1RA are not recommended. Close monitoring of therapeutic drug levels is encouraged as small studies report CNI dose reductions in combination with GLP1RA use, however a mechanism for drug interaction is unclear (2D).

SGLT2i:

Empiric adjustments to transplant immunosuppression with initiation of SGLT2i are not recommended (2B).

DPP4i:

Empiric adjustments to transplant immunosuppression with initiation of DPP4i are not recommended (2B).



Flowchart summarizing the reviewed evidence for novel antihyperglycemic therapies in PTDM with GRADE recomme

Figure 1. Guidance for Incorporation of Novel Antihyperglycemic Agents in Management of T2DM/PTDM in KTRs

CONCLUSION

This comprehensive review of the literature for use of novel antihyperglycemic agents in KTR with either T2DM or PTDM permitted meaningful conclusions surrounding existing data. In summary, GLP1RA agents appear to have similar impact on HbA1c and weight loss in KTR as the general patient population. Use of GLP1RA agents is often impacted by GI adverse effects, especially in the setting of

concomitant medications that also have GI adverse effects. More data are required to determine long term effects on cardiovascular outcomes. SGLT2i agents demonstrated comparable effects on HbA1c, eGFR, and weight in KTR as the general patient population. Positive results regarding blood pressure control seemed to be more unreliable in KTR compared to the general patient population. The most common adverse effect with SGLT2i agents in KTR was development of UTIs, which requires close monitoring in this immunosuppressed population, especially in the setting of more intense immunosuppressive states. DPP4i agents demonstrate the ability to reduce HbA1c in KTR in combination with other antihyperglycemic therapy with minimal risk of adverse effects. Management strategies are succinctly summarized within the algorithm (Figure 1) which demonstrates approaches for incorporation of novel antihyperglycemic agents.

It is important to note that while the provided guidance may be utilized to help direct clinical practice, this guidance is predominantly based upon small, retrospective studies and case series. Using the GRADE system recommendation, many of the summary statements are based upon moderate to very low quality of evidence and highly susceptible to change in confidence of estimated effect if prospective, randomized controlled data were to become available. Despite the limitations of existing data, the potential for these novel antihyperglycemic agents in KTR with T2DM or PTDM is promising. Multicenter, randomized, controlled studies in the solid organ transplant populations with these novel agents would significantly add to the recommendations provided, especially considering the significant need for data regarding initiation within the first year post transplant. As additional data emerges, especially with GLP1RA and SGLT2i agents, and potentially the newly available GLP1RA/glucose dependent insulinotropic polypeptide tirzepatide, these novel agents may end up proving to be, in the words of the Atlanta duo OutKast, “sweeter than a plate of yams with extra syrup.”[103]

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VISUAL ABSTRACT

Please reference Figure 1 for use as a potential visual abstract