REVIEW

Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors for diabetes after solid organ transplantation

Lale A. Ertuglu[1], Esteban Porrini[2,3,4], Mads Hornum[5,6], Atalay Demiray[1], Baris Afsar[7], Alberto Ortiz[8], Adrian Covic[9], Peter Rossing[6,10] & Mehmet Kanbay[11]

1 Department of Medicine, Koc University School of Medicine, Istanbul, Turkey
2 Red de Investigación Renal (REDINREN), Instituto Carlos III-FEDER, Tenerife, Spain
3 Department of Medicine, Hospital Universitario de Canarias, Tenerife, Spain
4 Instituto de Tecnologías Biomédicas, University of La Laguna, Tenerife, Spain
5 Department of Nephrology, Rigshospitalet, Copenhagen, Denmark
6 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
7 Division of Nephrology, Department of Internal Medicine, Suleyman Demirel University School of Medicine, Isparta, Turkey
8 IIS-Fundacion Jimenez Diaz, Department of Medicine, School of Medicine, Universidad Autonoma de Madrid, Madrid, Spain
9 Department of Nephrology, Grigore T. Popa' University of Medicine, Iasi, Romania
10 Steno Diabetes Center Copenhagen, Copenhagen, Denmark
11 Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey

Correspondence
Mehmet Kanbay MD, Division of Nephrology, Department of Medicine, Koc University School of Medicine, 34010, Istanbul, Turkey.
Tel.: +90 212 2508250;
fax: +90 850 2508250;
e-mails: drkanbay@yahoo.com, mkanbay@ku.edu.tr

SUMMARY

Post-transplant diabetes mellitus (PTDM) is a common complication of solid organ transplantation and a major cause of increased morbidity and mortality. Additionally, solid organ transplant patients may have pre-existent type 2 diabetes mellitus (T2DM). While insulin is the treatment of choice for hyperglycemia in the first weeks after transplantation, there is no preferred first line agent for long-term management of PTDM or pre-existent T2DM. Glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter 2 (SGLT2) inhibitors improve glycemic control, lower body weight, and blood pressure, are recommended after lifestyle and metformin as initial therapy for diabetic patients with cardiovascular or kidney comorbidities regarding their cardiorenal benefits. Furthermore, the mechanisms of action of GLP-1RA may counteract some of the driving forces for PTDM, as calcineurin-induced β cell toxicity as per preclinical data, and improve obesity. However, their use in the treatment of PTDM is currently limited by a paucity of data. Retrospective observational and small exploratory studies suggest that GLP-1RA effectively improve glycemic control and induce weight loss in patients with PTDM without interacting with commonly used immunosuppressive agents, although randomized-controlled clinical trials are required to confirm their safety and efficacy. In this narrative review, we evaluate the risk factors and pathogenesis of PTDM and compare the potential roles of GLP-1RA and SGLT2 inhibitors in PTDM prevention and management as well as in pre-existent T2DM, and providing a roadmap for evidence generation on newer antidiabetic drugs for solid organ transplantation.

Transplant International 2021; 34: 1341–1359

Key words
diabetes mellitus, glucagon-like peptide-1, kidney transplantation, post-transplant diabetes mellitus, SGLT2 inhibitors, solid organ transplantation

Received: 9 February 2021; Revision requested: 22 March 2021; Accepted: 12 April 2021;
Published online: 30 June 2021

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doi:10.1111/tri.13883

Introduction

Post-transplant diabetes mellitus (PTDM) is one of the most common complications of solid organ transplantation (SOT) with an incidence of 10–40% [1,2]. PTDM affects approximately 10–20% of kidney transplant recipients in the first year after transplant [1] and is associated with increased morbidity and mortality [3]. Although successful management of PTDM is key for improved outcomes in transplant patients, there is little scientific evidence advising transplant physicians how to expand the glucose-lowering treatment in PTDM patients on top of insulin. Additionally, SOT recipients may have pre-existent T2DM. In this narrative review, we evaluate the risk factors and pathogenesis of PTDM and the potential role of glucagon-like peptide 1 receptor agonists (GLP-1RA) in PTDM prevention and management as well as in pre-existent T2DM in SOT recipients, assessing their relative position versus sodium–glucose cotransporter 2 (SGLT2) inhibitors in cardio and renoprotective effects and benefits on survival and providing a roadmap for evidence generation on newer glucose-lowering drugs for solid organ transplantation.

PTDM diagnosis and incidence

The first guidelines on diagnostic criteria for new-onset diabetes after transplant (NODAT), which was later renamed as PTDM, were published in 2003 and recommended that the definition and diagnosis of diabetes after transplantation should be based on the accepted definition of diabetes mellitus and impaired glucose tolerance by the American Diabetes Association (ADA), World Health Organization (WHO), International Diabetes Federation (IDF), and American College of Endocrinology (ACE) [4]. A second international consensus decided that the diagnostic criteria for PTDM should follow those of the American Diabetes Association for the general population (Table 1) and focused on the timing of diagnosis [5]. Due to the high doses of corticosteroids in the early postoperative period, the consensus advised delaying the diagnosis of PTDM until patients are stable on maintenance immunosuppressive treatments [6].

PTDM pathogenesis: immunosuppressive drugs and other risk factors

The incidence of PTDM after kidney transplantation greatly varies depending on age, body mass index (BMI) and other risk factors in different study populations and ranges from 10% to 74%, although most recent reports range from 10% to 20% and the incidence may be higher for lung, heart and above all liver transplantation than after kidney transplantation [1,2,7,8].

PTDM incidence and pathogenesis

Both the traditional risk factors for T2DM, including age, obesity, family history of T2DM, African American race and Hispanic ethnicity [1,2], pretransplant metabolic syndrome, insulin resistance, prediabetes, obesity [9], and sedentary lifestyle [10] as well as transplant-specific risk factors predispose to PTDM, including the impact of immunosuppressive agents and history of rejection episodes.

Corticosteroids, which are well known to cause hyperglycemia and insulin resistance, are cornerstones of immunosuppression induction protocols at high doses and of maintenance protocols at low doses [11].

Calcineurin inhibitors (tacrolimus and cyclosporine) also increase the risk of developing PTDM. In a recent meta-analysis, the risk of PTDM was higher in tacrolimus than in cyclosporine users, with a relative risk of almost 2 [12]. The main mechanism is thought to be reduced insulin availability, based mainly on preclinical studies. Thus, calcineurin inhibitors decreased β-cell insulin content and decreased insulin secretion, induced β-cell apoptosis, and diminished β-cell proliferation, but also worsened insulin resistance [13–18]. Indeed, tacrolimus prevented insulin gene promoter activation by glucose or by changes in potassium ion concentration [15]. Furthermore, the primary calcineurin target, nuclear factor of activated T-cells (NFAT), regulates genes responsible for β-cell proliferation and insulin gene transcription [16]. Additionally, calcineurin inhibitors modulate β-cell transcription factors such as Forkhead box protein O1 and MafA [17]. Nevertheless, the effects of calcineurin inhibitors on glucose metabolism may be distinct for acute versus chronic exposure since several randomized clinical trials have showed an acute improvement in insulin sensitivity without any change in insulin secretion in response to calcineurin inhibitor treatment [19,20]. Thus, complex mechanism of the diabetogenicity of calcineurin inhibitors remains imperfectly understood.

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor used widely as immune suppressant after SOT, has also been associated with PTDM [21], possibly through effects on insulin signal transduction [3,22] or through changes similar to those observed with tacrolimus, since both drugs are linked to the same

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Table 1. American Diabetes Association diagnostic criteria for diabetes 2020.

Diabetes mellitus	Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l)* **OR** Hemoglobin A1C ≥6.5% (48 mmol/mol)† **OR** 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT‡ **OR** In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l)

*Fasting is defined as no caloric intake for at least 8 h.

†The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

‡OGTT, Oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water [115].

cyclophilin: FK506 binding protein-12 and tacrolimus inhibited mTOR in β-cells [23].

Solid organ transplantation-associated chronic inflammation may also contribute to the development of PTDM. Deceased donor grafts are associated with more severe inflammatory responses, which may contribute to the nearly threefold higher risk of PTDM in recipients of deceased grafts than in living donor grafts [24,25]. However, the intensity and components of the immunosuppressive regimens may have differed. Infections, namely hepatitis C virus and cytomegalovirus, are also associated with PTDM, especially after kidney transplantation [3].

Among traditional risk factors for the development of metabolic syndrome, T2DM and PTDM, obesity deserves special attention since it is also an independent predictor of chronic kidney disease (CKD) and its prevalence is 20% at the time of transplantation and may increase post-transplant diabetes [26]. Obesity in the first year post-transplant was associated with a significantly lower 5-year graft and patient survival, as well as higher rates of PTDM development (35% vs. 18%, $P = 0.02$) and cardiovascular disease (CVD) (32% vs. 18%, $P = 0.03$) [26].

GLP-1 receptor agonists

As PTDM is a major cause of morbidity and mortality in kidney transplant patients, including cardiac events and cardiac mortality, every effort should be considered to prevent and treat PTDM [1,2]. In nontransplant randomized clinical trials (RCTs), GLP-1RA showed promising cardio and kidney protection potential. In the next sections, we summarize GLP-1RA RCTS in nontransplant diabetes and information in SOT, with emphasis on kidney transplant patients with PTDM, as they represent the most common SOT modality.

Mechanism of action

Glucagon-like peptide 1 is an incretin hormone best known for its insulinotropic and weight lowering effects. GLP-1 lowers postprandial blood glucose levels via augmenting insulin and suppressing glucagon secretions, slowing gastric emptying and inducing satiety [27,28]. Consequently, GLP-1RA receptor agonists provide significant reductions in HbA1c levels of 0.3–1.9% [29], while also lowering blood pressure and improving dyslipidemia [30]; all of which are crucial factors related with the pathogenesis of cardiovascular disease and diabetic kidney disease [29]. Importantly, GLP-1-induced insulin secretion and glucagon inhibition are lost below fasting plasma glucose levels, preventing the development of hypoglycemia [31].

In vitro and animal studies provide further insight into the complex actions of GLP-1RA that may facilitate their various benefits. GLP-1 has been shown to stimulate pancreatic β-cell proliferation and survival [32] and promoted islet regeneration after partial pancreatectomy [33]. Moreover, GLP-1 induces satiety and reduces appetite at the level of central nervous system [34]. Preclinical evidence further corroborates the GLP-1RA-induced cardiorenal benefits that have been shown in randomized-controlled trials. While the mechanism of cardioprotection is not fully understood, it may be partially independent from its impact on glucose and lipid metabolism. In preclinical studies, cardiomyocytes express GLP1R [35,36] and nitric oxide-dependent mechanisms in the vasculature [30,37] may contribute to cardioprotection. GLP-1 also stimulates natriuresis, potentially by upregulating atrial natriuretic peptide (ANP) production [38], downregulating angiotensin II [39,40] and inhibiting the activity of sodium-hydrogen exchanger 3 (NHE3), resulting in decreased renin-

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angiotensin system (RAS) activation and decreased intraglomerular pressure [41]. Indeed, GLP-1RA treatment decreased renal cortical angiotensin II (Ang II) [42], ameliorated Ang II-induced renal [43] and cardiac fibrosis [44] in rats and reduced circulating Ang II levels in diabetic patients [45], although the mechanism of GLP-1RA induced RAS inhibition has not yet been clarified [46]. GLP-1 was also found to attenuate oxidative stress in both glomeruli and tubules via inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [47,48].

GLP-1RA available

Two families of GLP-1RA are commercially available: oral (Semaglutide) and parenteral (Liraglutide, Dulaglutide, Semaglutide, Albiglutide) GLP-1 analogues and exendin analogues (Exenatide and Lixisenatide) [49]. Exendin-4 is a peptide originally isolated from the venom of Heloderma suspectum (Gila monster) which is approximately 50% identical to GLP-1.

Randomized controlled trials in nontransplant diabetes

Clinically, some GLP-1RA improved primary cardiovascular outcomes and secondary renal outcomes in cardiovascular safety trials [49–52] (Table 2). Several large-scale trials established the cardiovascular safety and even benefit of GLP-1 analogues (except oral semaglutide), including decreased rates of fatal and nonfatal cardiovascular events [53–55] as well as death from any cause [53] (Table 2). However, oral semaglutide and exendin analogues, while safe from the cardiovascular point of

Table 2. Glucagon-like peptide-1 (GLP-1) receptor agonists and key cardiovascular safety trial results in type 2 diabetes mellitus patients without solid organ transplantation.

Family	Drug (trial)	Cardiovascular safety trial primary endpoint (3P-MACE) HR (95% CI; *P*)	Cardiovascular safety trial secondary kidney endpoint HR (95% CI; *P*)
GLP-1 analogue	Liraglutide (LEADER) [53]	0.87 (0.78–0.97; $P < 0.001$)	New-onset macroalbuminuria, sustained serum creatinine duplication, initiation of renal replacement therapy or renal death 0.78 (0.67–0.92; $P = 0.003$)
	Dulaglutide (REWIND) [55]	0.88 (0.79–0.99; $P = 0.026$)	New-onset macroalbuminuria, sustained decreased of eGFR <30% or the initiation of renal replacement therapy 0.85 (0.77–0.93, $P = 0.0004$)
	Semaglutide (SUSTAIN-6) [54]	0.74 (0.58–0.95; $P = 0.02$)	New-onset macroalbuminuria, doubling serum creatinine reaching an eGFR <45 ml/min/1.73 m^2, initiation of renal replacement therapy or renal death 0.64 (0.46–0.88; $P = 0.005$)
	Oral semaglutide (PIONEER-6) [116]	Neutral 0.79 (0.57–1.11)*	ND
	Albiglutide (HARMONY) [117]	0.78 (0.68–0.90; $P = 0.0006$)	ND
Exendin-4 analogue	Exenatide (EXSCEL) [118]	Neutral 0.91 (0.83–1.00)	40% reduction in eGFR loss, onset of dialysis or transplantation, renal death and onset of macroalbuminuria 0.85 (0.73–0.98; $P = 0.027$)
	Lixisenatide (ELIXA) [119]	Neutral 1.02 (0.89–1.17)	New-onset macroalbuminuria 0.81 (0.66–0.99; $P = 0.040$)

3P-MACE, 3-point MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke); eGFR, estimated glomerular filtration rate; ND, no data.

Updated from data presented in [49].

*$P < 0.001$ for noninferiority, $P = 0.17$ for superiority. Interestingly HR (95% CI) for death for death from any cause was 0.51 (0.31–0.84).

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view, did not display cardiovascular protection. A recent meta-analysis including the seven cardiovascular outcome trials reported that GLP-1RA decreased the risk of cardiovascular death by 12%, nonfatal stroke by 16%, hospitalization for heart failure by 9%, and all-cause mortality by 11% [56]. No significant impact on nonfatal myocardial infarction was observed. In line with the results of cardiovascular outcomes trials of GLP-1RA, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) now recommend the use of GLP-1RA with demonstrated cardiovascular benefit in T2DM patients with CVD after lifestyle and metformin therapy and encourages the consideration of GLP-1RA in patients with T2DM without established CVD who have indicators of high risk [57].

In addition to their cardioprotective benefits, some GLP-1RA may have renal benefits and delay or prevent the onset of macroalbuminuria [58] according to the secondary endpoints in cardiovascular safety trials. Improved renal outcomes were observed for both GLP-1 and exendin analogues in which it was tested (Table 2). A recent meta-analysis including the seven cardiovascular outcome trials reported that GLP-1RA decreased the risk of the composite kidney outcomes by 17%, although this was driven only by new albuminuria, which decreased by 24% [56]. Specifically, liraglutide [53], semaglutide [54], and dulaglutide [48,55] have been associated with lower rates of new or worsening nephropathy, while these benefits were directly related to the reduction in the progression of albuminuria [53–55]. The first dedicated renal outcome study with a GLP-1RA, the FLOW study, is testing whether parenteral semaglutide will protect against loss of kidney function and development of end-stage kidney disease (ESKD) (clinicaltrials.gov NCT03819153).

GLP-1RA target cardiorenal risk factors beyond hyperglycemia, such as body weight and systolic blood pressure. GLP-1RA treatment induced significant weight loss in both short- and long-term studies in both patients with and without T2DM [59]. In a meta-analysis including T2DM patients with BMI $\geq$25 kg/m^2 from 27 trials, mixed treatment comparison of GLP-1RA and other T2DM treatments or placebo revealed that GLP-1RA were the most successful treatment in terms of weight loss at 6 months. For instance, liraglutide resulted in a loss of 1.5 kg compared to placebo. No difference was found between different GLP-1RA [60]. In the LEADER trial, liraglutide caused a 2.3 kg weight loss over 3.8 years [53].

In another meta-analysis of 60 studies, GLP-1RAs were consistently associated with reduced systolic blood pressure (SBP), ranging from −1.84 to −4.60 mmHg compared to placebo, insulin, and sulfonylureas. However, diastolic blood pressure was not affected by GLP-1RAs except for exenatide, which caused a modest decrease [61].

The side effects of GLP-1RA are primarily gastrointestinal, specifically nausea, vomiting, and diarrhea and reported to occur in 10–50% of patients [62]. The high incidence of such adverse effects is associated with higher rates of treatment discontinuation than for SGLT2 or dipeptidyl peptidase 4 (DDP-4) inhibitors [63]. Hypoglycemia is seen rarely owing to the glucose-dependent activity of GLP-1 [62].

Rationale for GLP-1RA use in SOT

Based on clinical experience outside the transplant setting and limited SOT experience, as well as on preclinical data, GLP-1RA may address several key elements involved in the development and complications of PTDM (Fig. 1). First, GLP-1RA may prevent or delay the onset of PTDM by inducing weight loss and improving β-cell survival, insulin secretion, and insulin sensitivity. Importantly, most patients who develop PTDM beyond 12 months after transplantation had prior prediabetes [64]. Given that especially visceral fat is an independent predictor of PTDM [65,66], weight loss may be an important modifiable factor in the pathogenesis of PTDM. The regulatory effects of GLP-1RA on insulin and glucagon may be central in PTDM as they are in T2DM, since PTDM patients have impaired glucose-induced glucagon suppression and arginine-induced insulin secretion [67]. GLP-1RA may also reduce serum triglyceride levels [68,69] and counteract dyslipidemia triggered by mTOR inhibitors, which may induce severe hypertriglyceridemia [70]. A crucial factor for PTDM pathogenesis is calcineurin inhibitor toxicity. The results of several preclinical studies are promising for a protective effect of GLP-1RA against the diabetogenic effect of calcineurin inhibitors. In human islets transplanted into immunodeficient mice treated with tacrolimus or sirolimus, GLP-1RA completely prevented tacrolimus-induced β-cell dysfunction and partially prevented sirolimus-induced β cell dysfunction [71]. Additionally, GLP-1RA has a synergistic action with glucose to promote insulin gene transcription through NFAT [72] and rescued cultured human β-cell replication and survival as well as insulin release following calcineurin inhibition [73,74]. However, this is only so far supported by in vitro observations and clinical confirmation is required.

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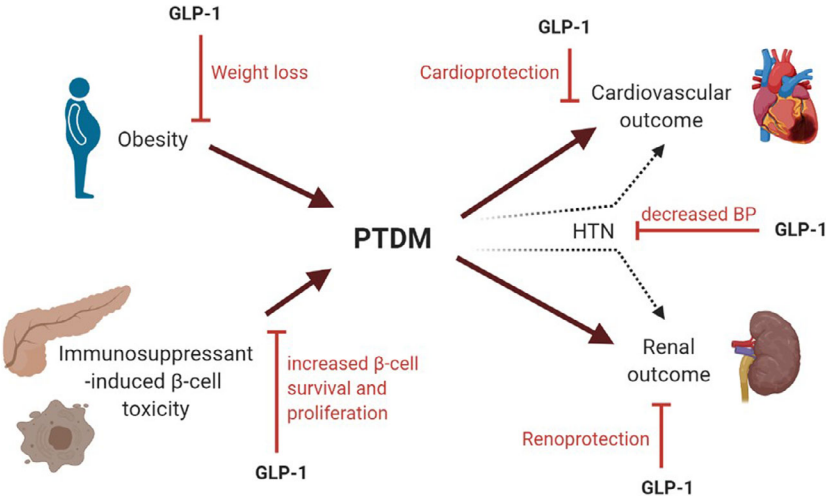

Figure 1 Postulated mechanisms of glucagon-like peptide-1 receptor agonists (GLP-1RA) in post-transplant diabetes mellitus (PTDM) based on results of clinical trials in general population type 2 diabetes, observational and exploratory studies in PTDM and solid organ transplant (SOT) recipients with type 2 diabetes mellitus and experimental data from human β-cells. Asterisks mark features that have been observed in SOT. Two families of GLP-1RA are commercially available: GLP-1 analogues (Liraglutide, Dulaglutide, Semaglutide, Albiglutide) and exendin analogues (Exenatide and Lixisenatide). So far, randomized-controlled trials in non-SOT patients have demonstrated cardiovascular protection for GLP-1 analogues but nor for exendin analogues. CVE, fatal and nonfatal cardiovascular events; UACR, urinary albumin:creatinine ratio.

Transplanted T2DM patients may also benefit from the already proven cardiovascular benefits of GLP-1RA as much as T2DM patients without transplants do. Thus, since cardiovascular complications in PTDM and T2DM share a common pathogenesis, GLP-1RA may also efficiently decrease the cardiovascular risk seen in PTDM and improve outcomes. Moreover, kidney protection by GLP-1RA may increase graft survival and improve kidney function in kidney transplantation recipients or even in other SOT recipients. Thus, hypertension, obesity, and poor glycemic control are risk factors for worsening kidney function in T2DM and possibly in PTDM and are targeted simultaneously by GLP-1RA. In this regard, except for exenatide and its extended release form, GLP-1RA are generally safe to be used in chronic kidney failure. While exenatide is eliminated from kidney and should not be used in patients with estimated glomerular filtration rate (eGFR) <30 ml/min [75], liraglutide, dulaglutide, and semaglutide are degraded by ubiquitous proteolysis pathways without a major organ of elimination [41], does not depend on kidney function for clearance [76] and does not require dose adjustments for CKD according to their labeling. Nevertheless, caution should be exerted for their use in severe renal impairment due to the lack of clinical evidence. Liraglutide, dulaglutide, and semaglutide are not dialyzable and there have been reports of increased plasma liraglutide concentrations and more gastrointestinal side effects in diabetic hemodialysis patients using liraglutide [77].

One major concern over the use of GLP-1RA in transplant patients is that they delay gastric emptying, thus potentially modifying the absorption of immunosuppressive agents, especially tacrolimus, which is a first line maintenance therapy in kidney transplantation. However, as discussed below, no evidence of a clinically significant impact has been uncovered so far.

Clinical experience with GLP-1RA for PTDM and pre-existent diabetes in SOT recipients

Little clinical experience exists in transplant patients with PTDM or pre-existing T2DM due to safety concerns and lack of clinical trials in this specific population. Several small ($n \leq 90$ per study for a total of <200 patients) short- to medium-term (up to 24 months) exploratory observational studies investigated some aspects of the efficacy and safety of GLP-1RA, mainly liraglutide and dulaglutide, in the management of PTDM as well as in transplant recipients with T2DM (Table 3). In this regard, a recent (updated 16 January 2020) Cochrane systematic review on glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients did not find any randomized controlled trial (RCT), quasi-RCT or cross-over studies examining head-to-head comparisons of active regimens of glucose-lowering therapy or active regimen compared with placebo/standard care of GLP-1RA [78]. Most patients in these studies were kidney transplant recipients.

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Table 3. Clinical characteristic of studies exploring GLP-1RA in solid organ transplant recipients with post-transplant diabetes mellitus or type 2 diabetes mellitus.

Study	Aim	Other used regimens	Case number	Pre-existent DM (*n*)	PTDM (*n*)	Weight loss	Kidney function	Tacrolimus	Side effects	Follow-up
Halden *et al*. [67]	Insulinotropic and glucagonostatic effects of GLP-1 on kidney transplant recipients with and without PTDM	Prednisolone, MMF, Tacrolimus, Cyclosporine Sitagliptin, Glimepiride, Glipizide, Metformin	24 (12 with PTDM 12 without PTDM)	0 (excluded)	12	NA	NA	NA	NA	NA
Pinelli *et al*. [79]	Short-term effects of liraglutide in kidney transplant recipients with PTDM	Tacrolimus, prednisolone	5	0 (excluded)	5	−2.1 ± 1.3 kg	NA	Unaltered trough concentration	Nausea, headache, injection site pain, weakness	21 days
Liou *et al*. [80]	Liraglutide in kidney transplant recipients with diabetes	Insulin, Metformin, Sulfonylurea, Alpha glucosidase inhibitor, DDP4i	7	NA	NA	−3 kg	No change	Unaltered trough concentration	Nausea, vomiting, headache, dizziness, rhinorrhea (*n* = 2s discontinued)	19.4 ± 7.6 months
Thangavelu *et al*. [81]	GLP-1RA* in SOT recipients with diabetes	Tacrolimus, prednisolone Insulin, Metformin, DDP4i, Sulfonylurea, SGLT2i	19	16	3	−4.9 kg	No change	Unaltered levels	Nausea and other gastrointestinal side effects (*n* = 3 discontinued)	12 months
Krisl *et al*. [82]	GLP-1RA† in SOT recipients with diabetes	Prednisolone, Tacrolimus, Cyclosporine, Everolimus	20	NA	NA	−6 ± 4 kg	No change	No change	Unspecified (no pancreatitis)	311 days
Singh *et al*. [83,84,87]	Liraglutide and dulaglutide in SOT recipients with diabetes	Tacrolimus, prednisolone Insulin	63 dulaglutide 25 liraglutide	NA	NA	−5.2% (dulaglutide) −0.89% (liraglutide)	+15% (dulaglutide) −8% (liraglutide) at 24 months	No dose adjustment required	Nausea, vomiting, diarrhea, abdominal pain nonsevere hypoglycemia cholelithiasis (liraglutide)	6–24 months
Kukla *et al*. [85]	GLP-1RA‡ in kidney transplant recipients with hyperglycemia	Tacrolimus, Everolimus, MMF, Prednisolone Insulin, Metformin, Glipizide	17	3	11	No change	No change	No change	One episode of acute pancreatitis Nausea, diarrhea Nonsevere hypoglycemia (*n* = 4 discontinued)	12 months

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Table 3. Continued.

Study	Aim	Other used regimens	Case number	Pre-existent DM (*n*)	PTDM (*n*)	Weight loss	Kidney function	Tacrolimus	Side effects	Follow-up
Cariou *et al.* [86]	Liraglutide, pancreas or pancreas–kidney transplant recipients	Tacrolimus, Cyclosporine, Everolimus, Prednisolone	6	NA	NA	−2.0 kg	No change	No dose adjustment required	Diarrhea, nausea, vomiting	6 months

BW, body weight; DPP4i, Dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MMF, mycophenolate mofetil; NA, not applicable; PTDM, post-transplant diabetes mellitus; SGLT, sodium–glucose transporter; SOT, solid organ transplant.

*Liraglutide (10 patients), dulaglutide (5 patients), exenatide and semaglutide (2 patients each).

†Liraglutide or exenatide.

‡Liraglutide (14 patients), dulaglutide (2 patients), exenatide (1 patient).

The insulinotropic and glucagonostatic effects of GLP-1RA are well known in T2DM patients, but there is less information in PTDM. Halden *et al.* compared the effects of a saline infusion versus GLP-1 during fasting and hyperglycemic conditions in 24 kidney transplant recipients with and without PTDM. Blood glucose, glucagon, and insulin concentrations were tested after fasting, a 3-h intravenous infusion of saline or GLP-1 and a 2-h hyperglycemic clamp initiated 1 h after the initiation of GLP-1 infusion. Despite similar fasting glucagon and insulin levels, glucose induced significantly less suppression of glucagon and less secretion of insulin in PTDM patients in the presence of a saline infusion (not shown). During the fasting state, GLP-1 decreased blood glucose to the same extent in both groups but decreased glucagon only in PTDM patients. During the hyperglycemic clamp, GLP-1 decreased glucagon and increased insulin secretion in both groups [67] (Fig. 2). These results confirmed that GLP-1 stimulates insulin secretion and attenuates glucagon secretion in PTDM, as it does in T2DM.

Pinelli *et al.* first reported the short-term use of a GLP-1RA in four kidney transplant patients with prediabetes or PTDM who concurrently used tacrolimus. Liraglutide did not modify trough tacrolimus concentration and the tacrolimus and maintenance corticosteroid doses remained unchanged through the 28-day follow-up. Acute kidney injury or acute rejection were not observed. Liraglutide was associated with a body weight reduction in all patients after 21 days (-2.1 ± 1.3 kg). Reported side effects included nausea, headache, and decreased appetite [79]. The study suggested that liraglutide may be a safe glucose-lowering drug in patients with PTDM with the added benefit of weight loss.

Several small retrospective studies investigated the safety and efficacy of GLP-1RA in the longer (6–24 months) term management of hyperglycemia in transplant patients, including but not limited to kidney transplant recipients.

In seven kidney transplant patients with poor glycemic control, liraglutide achieved fasting glucose control and hemoglobin A1c (HbA1c) levels dropped to 10.0 from 8.1% ($P = 0.032$). There was also significant weight loss of 3 kg and eGFR increased from 67.7 to 76.5 ml/min/1.73 m^2 ($P = 0.024$) during a mean follow-up of 20 months. Tacrolimus levels were not changed by liraglutide. However, of the seven patients, 2 (29%) discontinued the drug within 1 month due to side effects including nausea, vomiting, headache, and dizziness [80].

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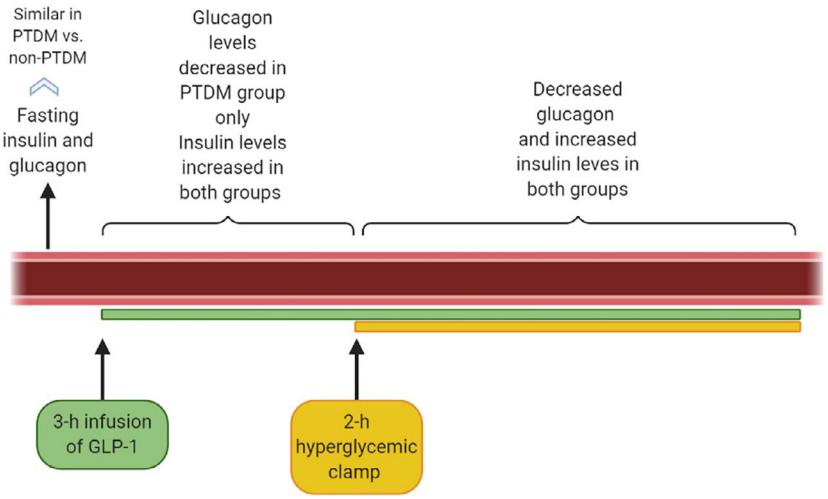

Figure 2 Impact of glucagon-like peptide-1 (GLP-1) on blood insulin and glucagon concentrations during fasting and hyperglycemic conditions in kidney transplant recipients with (continuous line) and without (discontinuous line) post-transplant diabetes mellitus (PTDM). Baseline pre-GLP-1 blood insulin and glucagon concentrations were similar in both groups. Conceptual figure based on data from [67].

Another retrospective study analyzed the effects of diverse GLP-1RAs (liraglutide, dulaglutide, exenatide, and semaglutide) in SOT recipients, including seven kidney, seven liver, and five heart transplant recipients. Patients had pre-existing (n = 16) or post-transplant (n = 3) diabetes and were followed for a mean of 12 months. GLP-1RA use was not associated with changes in tacrolimus levels or kidney function, while weight, BMI, and HbA1c decreased from baseline. Moreover, total cholesterol decreased by 26 mg/dl and low-density lipoprotein cholesterol by 21 mg/dl. A majority (n = 17) of patients were on insulin at baseline, while 2 were on oral medication only. In 57% of patients on insulin, insulin requirements had decreased at the end of 1 year [81]. Again, drop out was a major problem. Patients taking on GLP-1RA for <3 months were missed because of the study design. Additionally, 3 (16%) patients stopped the medication because of gastrointestinal-related adverse effects and two stopped because of cost (not covered by insurance or high co-pay), for a total of 26% dropout. The most common reported side effect was nausea in five patients.

An abstract report of a retrospective observation of 20 SOT recipients (seven kidney, one lung, six heart, three liver, and three multiorgan transplants) who had pre-existing DM or PTDM, reported HbA1c reduction and weight loss with the use of GLP-1RA (liraglutide or exenatide), without significant changes in serum tacrolimus and creatinine levels [82].

Singh *et al.* reported the effects of dulaglutide on 63 SOT recipients (51 kidney, 10 liver, one heart, one kidney, and liver) with diabetes pretransplantation (n = 43) or PTDM (n = 20) in another retrospective study. Dulaglutide use resulted in a loss 5.2 kg body weight and a decrease of 2 kg/m^2 BMI in 24 months. There was also a significant six units reduction in insulin requirements [83]. Information in dropout was incomplete, since only patients on dulaglutide for at least 6 months were enrolled. In this sense, 17 (21%) of the original 80 patients identified did not meet inclusion criteria. There was no comment on whether the reduction of the sample size of reported data to 59 (6 months), 49 (12 months), and 13 (24 months) may have been related to stopping the drugs for intolerance. The same group later compared the effects of dulaglutide (n = 63) vs. liraglutide (n = 25: 21 kidney, two liver–kidney, one liver, one heart) on SOT recipients. Approximately 8% of patients on liraglutide and 14% of patients on dulaglutide stopped all other glucose-lowering medications and were maintained only on GLP-1RA. Dulaglutide was associated with improvement in eGFR over 24 months as compared with liraglutide. However, the baseline characteristics of patients on liraglutide versus dulaglutide were not similar. The incidence of non-severe hypoglycemia (24% vs. 6.3%), rates of gastrointestinal side effects and numerical rates of cardiovascular events were higher on liraglutide than on dulaglutide. A major limitation of this report is that it remains unclear how many patients were followed for the full 2 years [84].

Kukla *et al.* retrospectively reviewed 17 patients with kidney transplant and either pre or post-transplant DM

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who were initiated on GLP1-RA:14 patients on liraglutide, 2 on dulaglutide and 1 on exenatide. Most (16 of 17) patients were on tacrolimus. GLP-1RA use was not associated with significant changes in tacrolimus dose, significant weight loss or HbA1c change at the end of 12 months. However, a significant reduction in total daily insulin dose was observed (median of 30 IU). Seven patients treated for 24 months had a weight loss of 8.6 kg at the end of follow-up. Kidney function remained stable throughout while 24 h urine protein excretion did not change significantly. No episodes of acute rejection were reported. Four (24%) patients discontinued the drugs due to side effects, which included an episode of acute pancreatitis and an additional patient because of poor glycemic control [85].

In a prospective case series, Cariou *et al.* examined the safety and efficacy of liraglutide on 6 pancreas transplant recipients, of whom 5 had simultaneous kidney transplantation. Patients with persistent hyperglycemia after the transplant were included and used only liraglutide as glucose-lowering treatment, while patients requiring insulin were excluded. A median decrease of 0.8% in HbA1c and of 2.0 kg in body weight were reported at 6 months. Liraglutide stimulated insulin secretion, as demonstrated by the increased C-peptide AUC (area under the curve) during oral glucose tolerance test (OGTT). Additionally, it decreased insulin resistance as assessed by a decrease in homeostatic model assessment for insulin resistance (HOMA–IR) score, even in patients that did not lose body weight. Tacrolimus and cyclosporine doses or kidney function did not change during liraglutide therapy, including in a patient with stage 3A CKD. Three patients experienced gastrointestinal symptoms and 1 (17%) consequently discontinued the drug [86].

Until now, no randomized clinical trials have tested GLP-1RA in transplant patients. A phase 2 randomized clinical trial sponsored by Mayo Clinic is currently underway to evaluate the efficacy and safety of exenatide for the treatment and prevention of PTDM in kidney transplant patients (clinicaltrials.gov NCT03961256).

Overall, these preliminary studies suggest that GLP-1RAs are safe and effective in glycemic control in post-transplant patients, including those on tacrolimus and/or corticosteroids, although larger randomized clinical trials are needed to establish long term outcomes and confirm potential benefits. However, an issue of gastrointestinal tolerance was identified in the available studies, leading to discontinuation rates as high as 30% that may have been underestimated based on the retrospective design and inclusion criteria. These discontinuation rates may be higher than those observed in the nontransplant population. Thus, permanent discontinuation of the trial regimen was 9.5% (vs. 7.3%) for liraglutide in cardiovascular safety trials, mainly due to gastrointestinal intolerance [53]. Given the low number of patients studied, PTDM was not differentiated from pretransplant T2DM in the currently available studies. Although GLP-1RA are potentially valuable in both patient populations and should be investigated for both populations, they differ in terms of pathogenesis and outcome endpoints. Hence, special attention should be given to distinguish PTDM from pre-existing T2DM in future studies.

GLP1-RA and nonkidney SOT

As outlined above, most experience with GLP-1RA is in the field of kidney transplantation and only a handful of patients with other forms of SOT have been reported [81–84,86,87]. This includes 13 patients with heart, 23 patients with liver, one with lung and five patients with pancreas transplantation [81–84,86,87]. Additionally, exenatide reduced insulin dose after 6 months in islet transplantation recipients requiring insulin therapy [88,89]. Overall, the results are reassuring and do not differ from those obtained in kidney transplant recipients, although the numbers are too low to make a definitive assessment.

GLP1-RA versus SGLT2 inhibitors for PTDM

SGLT2 inhibitors are the other major class of glucose-lowering drugs with demonstrated cardiovascular and kidney protective effects in large cardiovascular safety trials and for canagliflozin and dapagliflozin in CKD trials (CREDENCE and DAPA-CKD) [57,90–94]. Moreover, dapagliflozin offers kidney and cardiovascular protection in heart failure or CKD patients with or without T2DM [92–94]. Both CREDENCE and DAPA-CKD were stopped early by the safety monitoring committee because of the efficacy of SGLT2 inhibitors. They had hard primary outcomes including ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. These results are changing the routine management of CKD, as evidenced by recent guidelines and more that are expected to follow [95]. According to the latest update in 2019, ADA and EASD currently suggest SGLT2 inhibitors as first line choice for patients with T2DM and heart failure or CKD to reduce the risk of

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major cardiovascular events, death and progression of CKD [57].

Thus, SGLT2 inhibitors may be considered as alternative first line agents for PTDM and transplant recipients with pre-existent T2DM, although this hypothesis should be validated by clinical trials that confirm kidney and cardiovascular benefits as well as safety in this setting (Fig. 3; Table 4). It is crucial to note that SGLT2 inhibitors, which are contraindicated in patients with eGFR below 30 ml/min/1.73 m^2 and not recommended for patients with eGFR below 60 ml/min/1.73 m^2 [96], may not be a widely available treatment option for kidney transplant recipients, whose eGFR is below 60 ml/min/1.73 m^2 on average [97]. As their glucouretic effect diminishes progressively with decreasing renal function, SGLT2 exhibit dramatically lower efficacy in terms of glycemic control and HbA1c reduction in patients with CKD [98]. Consequently, the clinical significance of SGLT2 inhibitors in kidney transplant recipients is limited, although they remain a valid treatment option for kidney transplant patients with mild CKD and for other transplant recipients. Indeed, several studies investigated the utility of SGLT2 inhibitors in these populations. A recent (updated 16 January 2020) Cochrane systematic review on glucose-lowering agents for treating diabetes in kidney transplant recipients did not find any trial for GLP-1RA, but found a small study (n = 44) comparing SGLT2 inhibitors with placebo [78]. With low-moderate certainty evidence, they concluded that compared to placebo, SGLT2 inhibitors may reduce HbA1c without affecting fasting blood glucose and eGFR long-term and probably do not increase hypoglycemia, and have little or no effect on medication discontinuation due to adverse events, but probably do not affect kidney graft survival. However, all participants discontinuing SGLT2 inhibitors had urinary tract infections (UTI) [78]. In this regard, severe fungal emphysematous pyelonephritis in the kidney allograft caused by Candida glabrata, 3 weeks after starting treatment with empagliflozin and requiring urgent transplant nephrectomy was reported in a patient with prior history of repeated UTI [99]. A recent review in kidney transplant recipients concluded

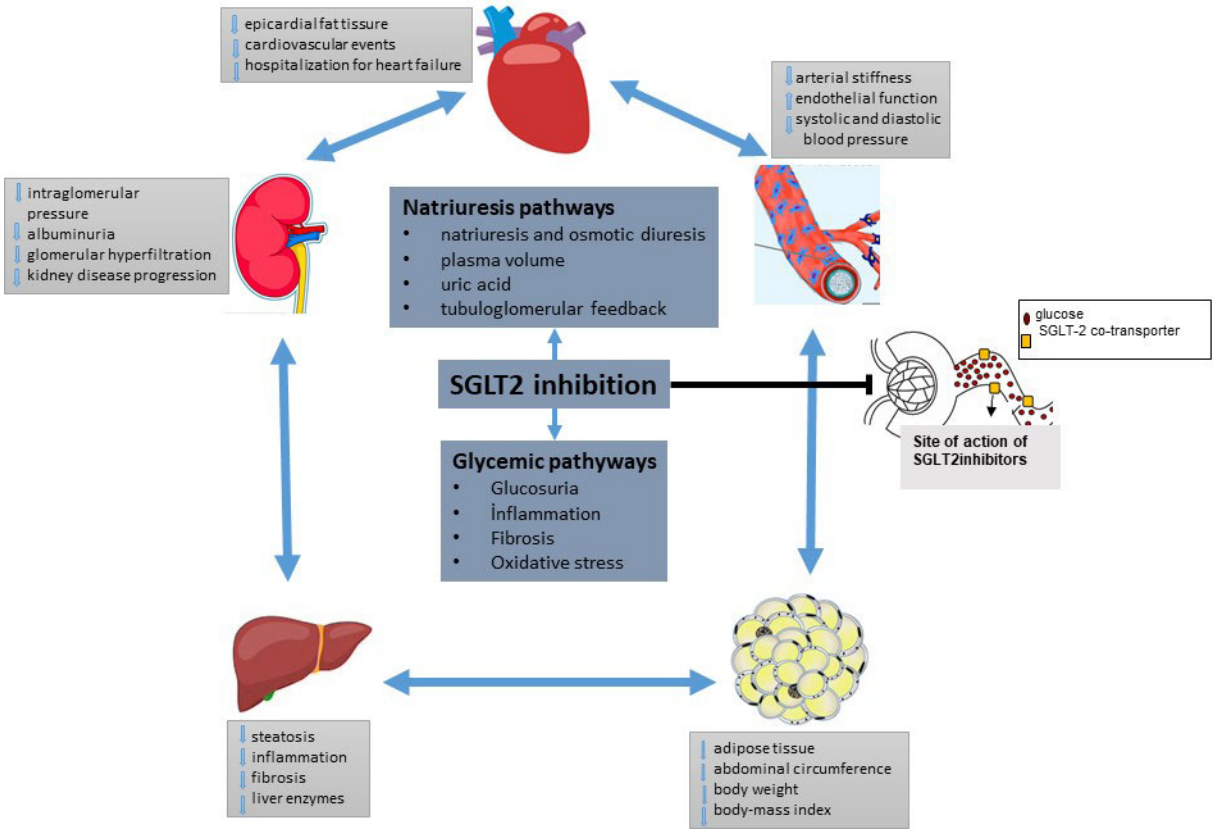

Figure 3 Metabolic and cardiorenal protective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors based on findings of clinical and experimental studies.

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Table 4. Glucagon-like peptide-1 receptor agonists (GLP-1RA) versus sodium–glucose transporter-2 (SGLT2) inhibitors in post-transplant diabetes mellitus (PTDM) and pre-existent type 2 diabetes mellitus (T2DM) in solid organ transplantation (SOT).

	GLP-1RA	SGLT2 inhibitors
General characteristics		
Route of administration	Usually parenteral	Oral
Frequency of administration	Daily to weekly	Daily
Mechanism of action	Primary: Increased insulin secretion, decreased glucagon concentrations and improve insulin sensitivity Increased satiety Possibly increased pancreatic β-cell proliferation survival Secondary: Decreased body weight	Primary: Induce glycosuria Secondary: Decreased body weight
Key efficacy outcomes		
Glycemia control	Yes	Yes (decreases as eGFR decreases)
Body weight	Decrease	Decrease
Blood pressure	Decrease	Decrease
Cardiovascular protection in cardiovascular safety trials In T2DM	Yes (GLP-1 analogues)	Yes
Cardiovascular protection in cardiovascular safety trials in nondiabetics	ND	Yes (heart failure)
Kidney protection in cardiovascular safety trials in T2DM	Yes	Yes
Kidney protection in CKD trials in T2DM	ND	Yes
Kidney protection in CKD trials in nondiabetics	ND	Yes
Key safety issues		
Key safety concerns	Gastrointestinal intolerance	Genitourinary infections, diabetic ketoacidosis, fractures? Amputations?
Main reason for discontinuation in published reports	Gastrointestinal intolerance	Severe or recurrent urinary tract infection
Key contraindication	Low eGFR for some drugs Family history of medullary thyroid carcinoma, multiple neoplasia syndrome type 2	Insulin deficiency, type 1 DM, eGFR <15–30 ml/min/1.73 m^2
Use in solid organ transplantation		
Primary mechanism of action expected to target PTDM pathogenesis	Yes (β-cell protection)	No
Published positive experience in SOT*		
Kidney	Yes (PTDM, T2DM)	Yes (PTDM, T2DM)
Heart	Yes (PTDM, T2DM)	Yes (PTDM, T2DM)
Liver	Yes (PTDM, T2DM)	No
Lung	Yes (PTDM, T2DM)	No
Pancreas	Yes (PTDM, T2DM)	Yes (PTDM)
RCTs in SOT	No	Yes

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ND, no data.

*PTDM or pre-existent T2D.

that there is evidence for safety with GLP-1 RAs, and SGLT2 inhibitors but also conceded that UTI and a slight initial decrease in kidney function may limit use of SGLT2 inhibitors and as compared with the non-transplant T2DM population, SGLT2 inhibitors may not be as efficacious in kidney transplant recipients [100]. By contrast, a systematic review through April 2020 identified 132 patients from 8 studies of SGLT2 inhibitors in kidney transplant patients with DM and concluded that among kidney transplant patients with

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excellent kidney function, SGLT2 inhibitors lower HbA1C, reduced body weight, and preserved kidney function without reporting of serious adverse events, including euglycemic ketoacidosis and acute rejection [101]. Thus, an early 2017 report on 80 person-months of follow-up in four pancreas–kidney and six kidney transplant recipients on SGLT2 inhibitors suggested safety and no significant adverse effects but no significant impact on HbA1C or weight or other parameters [102]. An early small prospective study of empagliflozin on PTDM in kidney transplant recipients was disappointing: two of 14 (14%) dropped out for recurrent UTI within 12 months, two more for inadequate glycemic control and two because of loss of GFR (one for acute rejection) for a total of 43% stopping the medication in less than 12 months [103]. In the above-mentioned placebo controlled RCT in PTDM for 6 months, one patient stopped SGLT2 inhibitors because of urosepsis for an incidence of 1/132 patient-months [104]. Other smaller reports overall observed decrease HbA1C, weight/BMI and systolic blood pressure, stable kidney function and/or immunosuppressive drug levels, but 1 in 26 stopped the drug because of recurrent UTI, even when at least some studies had excluded patients with prior UTI [105–108]. A series of 22 heart transplant recipients also observed reductions in weight/BMI, HbA1c, and furosemide dose that were not seen in a control group and one patient stopped because of acute kidney injury [109]. We found no reported experience with liver or lung transplant recipients. Of interest, SGLT2 inhibitor-stimulated rise in endogenous glucose production is strongly related to the increase in urinary glucose excretion, blunting the decline in fasting plasma glucose [110]. This mechanism may be compromised in injured livers

In summary, clinical experience with SGLT2 inhibitors in PTDM or pre-existing T2DM in SOT is more limited than for GLP-1RA in terms of number of patients and patient-months reported and of type of SOT, although the availability of a small RCT implies a higher level of evidence. Overall, these reports suggest efficacy in at least some patients as well as weight loss and blood pressure lowering but the discontinuation rate was high in studies whose design allowed evaluating this parameter and most worrisome, in at least some patients discontinuation was driven by potentially severe UTIs with the need for nephrectomy having already been reported. It is noteworthy that while the main cause of discontinuation of GLP-1RA in the available studies was gastrointestinal intolerance, most pertinent

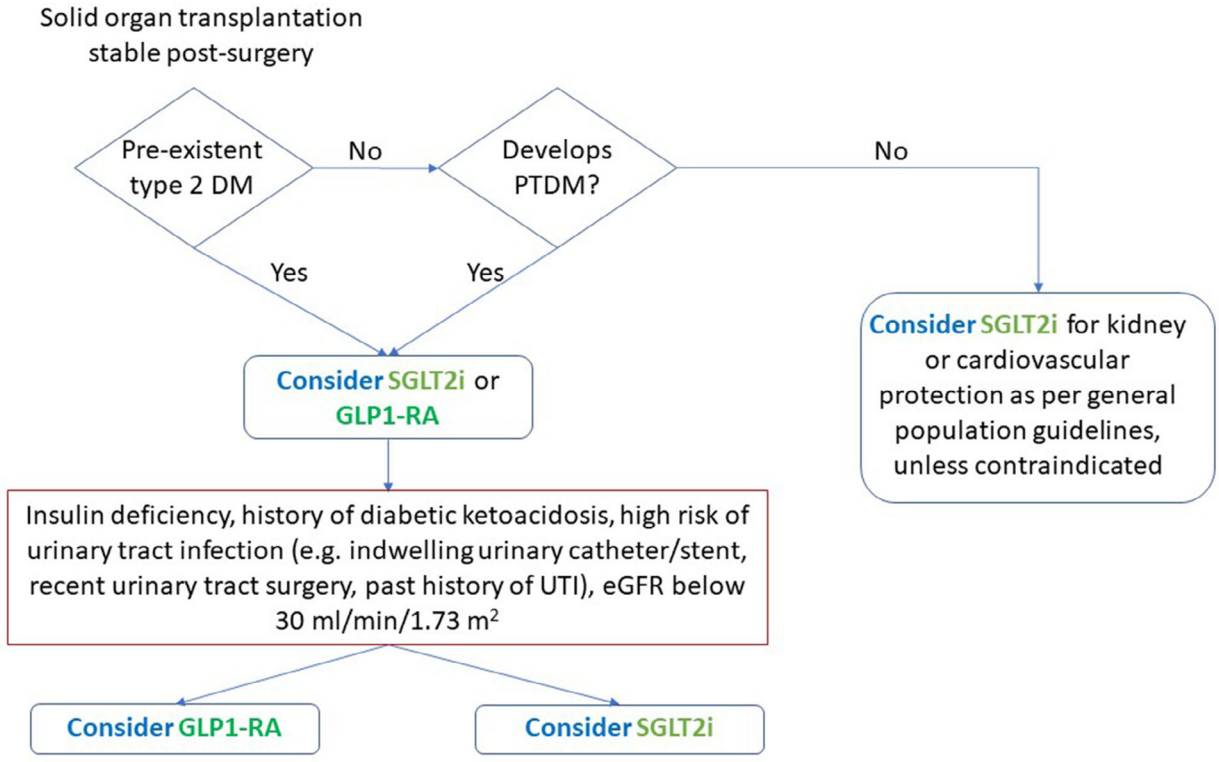

Figure 4 Therapeutic algorithm based on potential advantages and disadvantages of glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter 2 (SGLT2) inhibitors.

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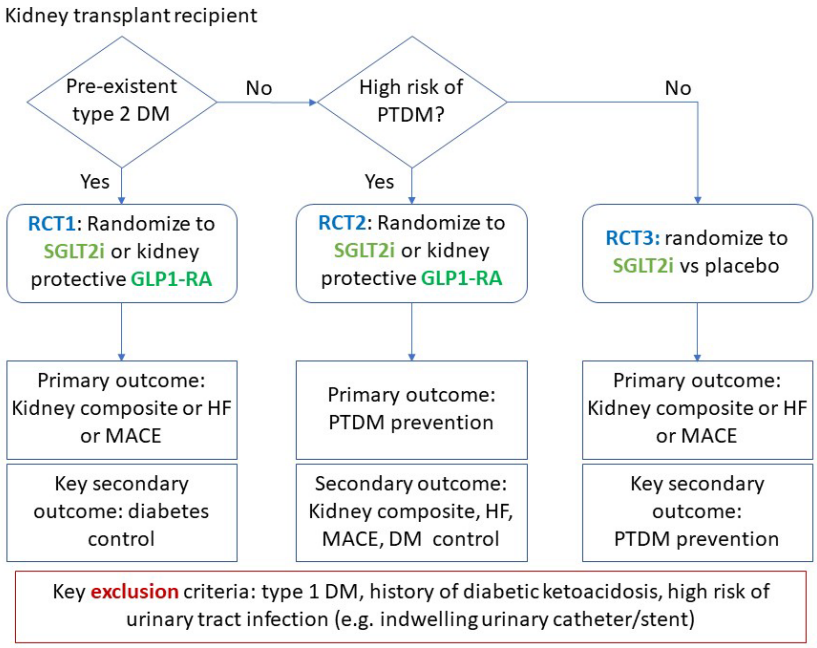

Figure 5 Roadmap for randomized clinical trials (RCTs) testing novel antidiabetic agents with kidney and cardiovascular protective actions in solid organ transplant (SOT) recipients with diabetes mellitus (DM). *Both certain glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter 2 (SGLT2) inhibitors (SGLT2i) have demonstrated cardiovascular and or kidney protective effects in clinical trials in general population patients with type 2 diabetes and, for SGLT2i, in nondiabetic patients with chronic kidney disease (CKD) or heart failure (HF). This is coupled with additional benefits that may contribute to prevent post-transplant diabetes mellitus (PTDM). These include weight loss as evidenced in clinical trials as well as preclinical evidence of protective effects of GLP-1RA on insulin-secreting islet cells. However, only well designed and optimally sized randomized-controlled trials (RCTs) will provide the evidence for evidence-based recommendations for the choice between GLP-1RA or SGLT2i for SOT recipients. We suggest a roadmap for RCT design and eligible populations to address this issue. RCTs would start after patient stabilization in the post-transplant period. A first proposal would be to test the first line use of these agents as antidiabetic agents in patients already having a diagnosis of type 2 diabetes, in a protocol calling for addition of other antidiabetic agents if glucose control is suboptimal. A second proposal for nondiabetic individuals at high risk of PTDM, GLP-1RA or SGLT2i would be the only antidiabetic agents prescribed until PTDM develops and cannot be adequately controlled by GLP-1RA or SGLT2i. A third trial may enroll nondiabetic patients at low PTDM risk to assess kidney and cardiovascular protection of SGLT2 inhibitors versus placebo, based on general population RCT results in nondiabetic patients with heart failure or CKD. In this trial, there would not be an arm for GLP-1RA, unless safety and efficacy in nondiabetic patients is shown first in the general population. MACE: major atherosclerotic cardiovascular events. Composite kidney endpoint defined as per prior GLP-1RA or SGLT2i RCTs as end-stage kidney disease, renal replacement therapy, kidney death or a choice between doubling of serum creatinine or a decrease of 40–50% in estimated glomerular filtration rate. The proposed roadmap would allow to enroll most eligible kidney transplant recipients in these RCTs and have answers to the research question of whether these strategies improve patient outcomes within 5–10 years.

cause of cessation of SGLT2 inhibitors was UTI, a potentially serious adverse effect for transplant patients who are immunocompromised. As an additional consideration, whether and how SGLT2 inhibitors may affect the pathogenesis of PTDM and its drivers is unclear, as the acute administration of dapagliflozin did not modify plasma insulin, C-peptide, glucagon in kidney transplant recipients without DM [111]. In this regard, dapagliflozin had no effect on glucagon or insulin secretion by human islets at either high or low glucose concentrations and did not alter human insulin and total glucagon levels in mice bearing transplanted human islets nor it modified human islet graft hormone content, endocrine cell proliferation or apoptosis [112]. Nevertheless, large randomized clinical trials are required to reach a definitive conclusion on the efficacy and safety of SGLT2 inhibitors in transplant population.

Conclusion and roadmap

PTDM is a common consequence of SOT and an important cause of poor outcomes. Additionally, T2DM is a major cause of ESKD and a frequent occurrence in kidney transplant recipients. While several GLP-1RA

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improve cardiovascular and kidney outcomes in T2DM, their safety and efficacy have not yet been verified in transplant patients with PTDM or pre-existing T2DM. However, they may have advantages over conventional glucose-lowering drugs since, as SGLT2 inhibitors, they improve cardiovascular and kidney outcomes in general population patients. SGLT2 inhibitors may also improve additional risk factors such as overweight and hypertension. Furthermore, preclinical studies on GLP-1RA suggest that their mechanism of action may counteract basic drivers of immunosuppressant-induced β-cell dysfunction. Finally, although both GLP-1RA and SGLT2 inhibitors have relatively high discontinuation rates in SOT, this is due to gastrointestinal intolerance rather to safety concerns in the case of GLP-1RA. According to limited data from retrospective and small exploratory analyses, GLP-1RA do not alter serum tacrolimus and eGFR levels while effectively maintaining normoglycemia and reducing body weight. Randomized, controlled clinical trials are warranted to assess the safety and efficacy of GLP-1RA and SGLT2 inhibitors in preventing PTDM and/or the management of PTDM and T2DM in SOT patients and their impact on cardiovascular and kidney outcomes. Given that more than 75% of PTDM cases arise within the first 3 months after transplantation [1], we anticipate that prompt initiation of these agents after the diagnosis of PTDM may provide the most benefit for long term outcomes, while early initiation of GLP-1RA may also have the potential to ameliorate tacrolimus-induced toxicity. Nevertheless, studies are also needed to verify the ideal timing for the use of GLP-1RA and SGLT2 inhibitors after transplantation. For patients with pre-existing DM, insulin is the preferred therapy for the first 1–2 months post-transplantation and oral agents can be considered after the doses of immunosuppressant drugs are stabilized [1]. In patients with predisposing factors, early preventive strategies to reduce the risk of PTDM should focus on lifestyle modifications, which can potentially reverse impaired glucose tolerance in post-transplant patients [113].

It is crucial to note that the current evidence on the use and safety of SGLP-1RA in transplant patients relies solely on observational studies and randomized clinical trials are required before any specific recommendation can be made. In the future research, kidney transplant patients should be particularly studied as they represent the most common SOT population and at a high cardiovascular and kidney risk that may potentially obtain extra benefits from GLP-1RA or SGLT2 inhibitors. The definition of reliable predictors of PTDM that allow the study of the value of GLP-1RA or SGLT2 inhibitors in the prevention of PTDM in high-risk patients is a further area of research. Since age, high plasma glucose levels on post-transplant day five and high baseline BMI predict the development of PTDM [114], these or similar risk factor may be used to enrich the trial population in risk for PTDM and test the impact of GLP-1RA or SGLT2 inhibitors on PTDM prevention. Figure 4 presents an algorithm for choice between GLP-1RA and SGLT2 inhibitors for SOT patients with PTDM or pre-existent type 2 DM based on the efficacy and safety profile of both agents. However, it should be noted that these data have been obtained mainly from non-SOT population data. Thus, Fig. 5 presents a roadmap to generate the necessary evidence for a rationale choice of glucose-lowering agent in SOT. Given that kidney transplantation is the most common SOT worldwide and that diabetes is a common cause for the need for kidney transplantation and a complication of kidney transplantation, we suggest this population will provide the greatest feasibility for clinical trials. Furthermore, given the evidence of benefit obtained in non-SOT trials, we propose that GLP-1RA should be tested against SGLT2 inhibitors rather than against conventional glucose-lowering drugs. In this regard, the efficacy shown in RCTs in individuals with or without DM with either CKD or heart failure, SGLT2 inhibitors are becoming part of the standard of care for these conditions, independent from the presence of diabetes and, thus, are a natural comparator for GLP-1RA.

Funding

This study was not funded by any grant.

Conflict of interest

PR: honoraria for consulting and teaching to Steno Diabetes Center Copenhagen from Astellas, Astra Zeneca, Boehringer Ingelheim, Bayer, NovoNordisk, Sanofi, Gilead, Merck, Vifor. AO: honoraria for consulting and speaker fees from Astra Zeneca, Sanofi, Vifor, Mundipharma. The other authors declare that they have no conflict of interest.

Acknowledgements

M.K. gratefully acknowledges use of the services and facilities of the Koc University Research Center for Translational Medicine (KUTTAM), funded by the Presidency

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of Turkey, Presidency of Strategy and Budget. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Presidency of Strategy and Budget." E.P. is a researcher of the Program Ramon y Cajal (RYC-2014-16573).

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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