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Diabetes in kidney transplantation

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Short title: Diabetes and transplant

1. Abstract

Diabetes mellitus (DM) is one of the most common complications after kidney transplantation and is associated with unfavorable outcomes including death. DM can be present before transplant but post-transplant diabetes mellitus (PTDM) refers to diabetes that is diagnosed following solid organ transplantation. Despite its high prevalence, optimal treatment to prevent complications of PTDM are unknown. Medical therapy of pre-existent DM or PTDM after transplant is challenging due to frequent interactions between antidiabetic and immunosuppressive agents. There is also frequent need for medication dose adjustments due to residual kidney disease and a higher risk of medication side effects in patients treated with immunosuppressive agents. Sodium glucose 2 inhibitors (SGLT2-i) have demonstrated a favorable cardio-renal profile in patients with DM without a transplant and hence hold great promise in this patient population although there is concern about the higher risk of urinary tract infections. The significant gaps in our understanding of the pathophysiology, diagnosis and management of diabetes mellitus after kidney transplantation need to be urgently addressed.

2. Clinical summary

a. Diabetes mellitus after transplant, which includes pre-existing diabetes and post-transplant diabetes, is extremely common and is associated with increased morbidity and mortality.

b. The pathogenesis of post-transplant diabetes shares similarities with other subgroups of type 2 diabetes. However, PTDM presents distinct drivers for metabolic dysfunction including calcineurin inhibitor toxicity to the pancreatic beta cell, thus making PTDM a separate entity.

c. Fasting glucose and hemoglobin A1c may not reflect the altered metabolism after an organ transplant making the diagnosis of PTDM more challenging. Oral glucose tolerance test should be considered the gold standard for its diagnosis.

d. Optimal treatments goals in PTDM are unknown.

e. SGLT2-i have demonstrated efficacy and safety in the treatment of non-transplant related DM with improvement in cardiovascular risk and decrease in kidney disease progression. However, SGLT2-i therapy post-kidney transplant may pose a substantially higher risk of genitourinary infections and vasomotor acute kidney injury. Studies to determine whether SGLT2-i provide clinical benefits including cardiovascular prevention and nephroprotective effects are need post-transplant.

3. Introduction

DM is a common complication of kidney transplantation. In the US, almost 50% of the incident end stage kidney disease patients have DM and diabetes is the primary cause of kidney disease in 22% of kidney transplant recipients[1]. Furthermore,-2 to 50% of patients that did not have DM before kidney transplant, will develop it post-transplant[2]. DM in a kidney transplant recipient is associated with significant morbidity and mortality independently of whether it was present pre-transplant. Diabetic kidney transplant recipients have reduced overall survival[3] with increased cardiovascular complications and infections.

Despite its high prevalence and association with poor outcomes, optimal management strategies for DM after kidney transplant are unknown. Interactions between immunosuppressive medications and anti-diabetic agents make its treatment challenging. The persistence of chronic kidney disease (CKD), high frequency of episodes of acute kidney injury (AKI) and worsening kidney function also complicates therapy.

The current review will focus on the burden of type 2 diabetes (T2DM) after transplant with a brief discussion on the treatment of type 1 diabetes (T1DM). We will review the epidemiology and pathogenesis of PTDM, the diagnostic challenges, risk factors and outcomes as well as management strategies.

4. Post-transplant diabetes mellitus

a. Definition

PTDM refers to diabetes mellitus that is diagnosed after kidney transplant, and acknowledges that some patients may have had undiagnosed pre-transplant DM. This is in contrast to the old nomenclature of new onset diabetes after transplant (NODAT) that assumed that the patients did not have DM prior to transplant. Currently, it is estimated that up to 10% of patients with the diagnosis of PTDM have undiagnosed diabetes pre-kidney transplantation[4].

b. Incidence.

The scientific literature reports wide variations in the prevalence of DM after transplant, which is partly due to a lack of historic consistent criteria for its diagnosis. In 2003 consensus guidelines were published to aid in the diagnosis of diabetes mellitus after transplant[5] and more contemporary series using the guideline's criteria reflect a PTDM prevalence of 10-30%[6,7]. The incidence of PTDM is higher in non-kidney organ transplant recipients. Incidence of PTDM in heart transplant recipients ranges between 20-30%, in liver transplant recipients 20-40% and lung transplant recipients 20-40%[8].

c. Diagnosis

The diagnosis of PTDM relies on the same criteria that are used to diagnose DM in the non-transplant population[9]. In brief, diabetes mellitus after kidney transplant is diagnosed if fasting glucose ≥ 126 mg/dL (7 mmol/L) on more than one occasion, random glucose ≥ 200 mg/dL (11.1 mmol/L) with symptoms, or a 2-hour glucose level after a 75-g oral glucose tolerance test (OGTT) ≥ 200 mg/dL (11.1 mmol/L). OGTT is

more sensitive than fasting glucose alone and should be considered the gold standard for the early diagnosis of PTDM since PTDM presents often with postprandial hyperglycemia and normal fasting glucose levels[10,11]. In 2013 a panel of transplant nephrologists, surgeons, diabetologists, and clinical scientists reviewed and updated the criteria for PTDM. The review clarified issues specific to transplant recipients[12] such as the use of hemoglobin A1c (HbA1c) and proposed standard PTDM nomenclature. Some key points from the consensus conference will be highlighted here.

Short term hyperglycemia is common in the immediate post-transplant period and is attributable in part to different post-surgical stressors such as inflammation, use of high dose steroids for the induction of immunosuppression, infections and a high frequency of enteral or parenteral nutrition[13,14]. As a result, in order to ensure a uniform and consistent diagnosis of PTDM, it was proposed that the diagnosis should be made when allograft function and immunosuppression levels are stable, and other perioperative complications (e.g. infection and/or rejection) are resolved.

OGTT should remain the gold standard for the diagnosis of PTDM as it is more sensitive than relying exclusively on fasting glucose levels [10,11]. OGTT also screens for impaired glucose tolerance (IGT) which is not only a risk factor for development of PTDM but is also an independent risk factor for cardiovascular disease and mortality [15,16]. Despite its value, OGTT is not used widely in clinical practice due to need for more resources.

HbA1c levels in the early post-transplant period are unreliable, especially if low. After transplant, erythropoiesis is reduced with immunosuppressive medications and the persistence of kidney disease driving anemia. Treatment of anemia often requires erythropoietin analogs which will alter red blood cell survival. Post-transplant transfusions may also influence HbA1C levels. Due to changes in red cell turnover, hemoglobin concentration, and even glucose concentration in the early post-transplant period, a normal HbA1c does not exclude PTDM[17]. On the other hand, glycosylated hemoglobin levels between 5.7 and

6.4% in the early post-transplant period or with anemia, may reflect the need to perform an OGTT since it is the best diagnostic tool and should alert us to the possibility of PTDM.

After the 2013 consensus meeting, most subsequent transplant guidelines advocate screening for PTDM with fasting blood sampling and HbA1c to determine the patients at risk who will benefit from an OGTT.

d. Risk factors

Risk factors for the development of PTDM are similar to those that increase the risk prior to transplantation, however, transplant specific risks also contribute (**Table 1**). The use of immunosuppressive medications including calcineurin inhibitors (CNIs), steroids and mammalian target of rapamycin (mTOR) inhibitors, infections such as hepatitis C, and hypomagnesemia are specific factors associated with increased risk of PTDM. CNIs, which include tacrolimus (Tac) and cyclosporine (CSA), are the cornerstone of immunosuppressive therapy, and are more commonly used than mTOR inhibitors such as sirolimus or everolimus. CNIs promote PTDM by inhibiting crucial signaling pathways for pancreatic β-cell growth and function[18]. The diabetogenic potential of CNIs is dose dependent[19] and Tac is considered more diabetogenic than CSA[20]. mTOR inhibitors are also associated with development of PTDM at higher rates than CSA but at lower rates than Tac[21]. Weight gain, which induces insulin resistance, is another factor that is more prevalent in post-transplant patients. Significant weight gain after kidney transplantation is common, as a consequence of the use of steroids and the dissipation of uremic anorexia. Counseling on appropriate weight management and healthy habits should be part of the post-transplant counseling and avoidance of weight gain may reduce risk of PTDM.

e. Pathogenesis

PTDM shares multiple pathophysiological characteristics with pre-transplant DM but, since PTDM has distinct mechanisms that eventually lead to hyperglycemia, is now considered a separate entity. As in pre-transplant DM, PTDM presents dysfunctional insulin sensitivity (IS)[22,23], abnormal insulin production with

pancreatic β-cell dysfunction[24,25], lack of glucagon suppression with hyperglycemia[26], as well as hypertriglyceridemia, obesity, and low-grade inflammation[27,28]. The dominant mechanism that leads to the development of PTDM is still an area of debate although several groups propose that β-cell dysfunction is the main pathophysiological process[10,11,24,25]. The role of insulin resistance in the development of PTDM is less clear as timing and methods used for evaluation of insulin sensitivity vary widely between studies [29]. One way to explain the post-transplant differences observed could be the fact that insulin sensitivity is a dynamic process that changes significantly over time. This possibility was examined by Hjelmesaethh et al.[30,31] who studied insulin sensitivity by OGTT and insulin measurements at 10 weeks, 1 year, and 6 years post renal transplantation. Early post-transplant patients had decreased insulin sensitivity and defects in insulin secretion. The magnitude of the defect on insulin sensitivity and secretion correlated with the glucose tolerance state and development of PTDM. Between 1- and 6-years post-transplant, patients with PTDM continue to have significant reduction of insulin secretion but no longer show significant differences in insulin sensitivity compared to patients with normal glucose tolerance. Data from these studies may reflect the fact that defects in insulin secretion after transplant are more constant, most likely due to the persistent use of β-cell toxic immunosuppression whereas insulin sensitivity can vary more widely. More recently, alterations in the incretin axis between the gut and pancreas have also been demonstrated in patients with PTDM. Patients with DM have a defect in the incretin system with decreased insulin and increased glucagon release in response to a glucose load that improves with glucagon-like peptide 1 (GLP1) agonist treatment. Patients with PTDM, like those with DM unrelated to transplantation, have reduced glucose-induced insulin secretion and attenuated glucagon suppression when studied with the hyperglycemic clamp, the gold standard test to assess insulin secretion capacity and beta cell response to glucose. In this study, GLP1 infusion also improved insulin and glucagon responses to hyperglycemia in patients with PTDM[26].

f. Outcomes/Complications

DM pre- or post-transplant is associated with increased morbidity and mortality. Similarly to T2DM, development of PTDM is associated with a significant increase in cardiovascular disease[32-34] risk and death[7,14,35]. Specifically, PTDM is associated with a 60% increase in post-transplantation myocardial infarction[36], increased risk of cerebrovascular accidents[33], as well as aortic or lower extremity arterial disease[33,34]. Interestingly, despite the higher mortality risk, graft viability is not impacted by PTDM since death censored graft loss does not differ[16]. Besides the increased risk of macrovascular disease and death with development of PTDM, these patients may also develop microvascular disease related complications at an accelerated rate[37]. The risk of increased morbidity and mortality with PTDM has also been demonstrated in pre-diabetic states including impaired glucose tolerance and impaired fasting glucose[15,38]. To summarize, PTDM and its precursor states are associated with poor outcomes including a higher risk of microvascular and macrovascular disease although graft survival is not affected.

5. Management of diabetes mellitus after transplant

Management strategies for treatment of PTDM should aim to improve β- cell function and decrease insulin resistance.

In contrast with T2DM, there are no specific glucose or A1c targets for the treatment of PTDM as there is no data on the degree of glycemic control that is associated with reduction of complications after development of PTDM[39]. Despite this, most transplant centers will aim for HbA1c of 7-7.5% as suggested in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the management of transplant recipients[40]. Due to the possibility that diabetic complications occur early after transplant[37] and lead to poor outcomes, we advocate treating PTDM aggressively and promptly after diagnosis making every effort to avoid hypoglycemia. On the other hand, it is reasonable to consider higher thresholds for older and debilitated patients.

a. Lifestyle changes and bariatric surgery.

Lifestyle modifications should be emphasized as one of the initial treatments of PTDM since a combination of exercise and weight loss improves insulin sensitivity and β-cell function in diabetic patients[41,42] although its effectiveness in PTDM is limited to a few small studies. A combined approach to diet and weight loss have shown complete reversal of impaired glucose tolerance after 6 months post-transplant in a non-randomized study[43] whereas a randomized control trial of active versus passive lifestyle interventions was only able to show improvement in weight loss and reduction of fat mass without improvement in glucose metabolism[44]. Unfortunately, more data are needed to determine the real effect of lifestyle modifications to prevent development of PTDM. The role of bariatric surgery before or after kidney transplantation to decrease the risk of PTDM is also underexplored, with just a few reports citing the experience of individual centers in a small number of patients[45-47]. Due to the evolution and improvement of bariatric surgery techniques, excellent outcomes and safety profile in the general non – transplant population and growing data from the transplant population[48], bariatric surgery could be considered for a select population depending on the risk factor profile and expected time to transplantation.

b. Antidiabetic medications

A recent review by Cohen et al.[49] summarizes therapeutic studies in the context of PTDM and highlights the paucity of available data. Older drugs such as the biguanide metformin, secretagogues such as glipizide and repaglinide as well as thiazolidinediones have been used for the treatment of PTDM and have demonstrated safety, low drug to drug interactions with immunosuppressive medications and efficacy in lowering blood glucose. It is important to remember that CNIs are metabolized via cytochrome p450 3A4 (CYP3A4) so drugs that interact with the CYP3A4 pathway can significantly alter CNIs drug levels. At the time of starting antidiabetic treatment several issues should be considered: a) drug to drug interactions, b) exacerbation of the side effects of immunosuppressant medications when used concomitantly with oral antidiabetic therapies with similar side effects, and c) kidney clearance of the different drugs as transplant patients will have different degrees of residual kidney disease.

i. Post-surgical period

Insulin is the main antidiabetic medication used in the immediate post-transplant period. Data from a small proof of concept study showed that patients with blood glucose >140 mg/dL treated with insulin early post-transplantation had decreased risk of PTDM compared to patients treated with oral antidiabetic agents. The study proposed early insulin therapy to protect β-cell function toxicity from hyperglycemia and decrease PTDM incidence[14]. A large randomized control trial, the ITP-NODAT trial (Early postoperative basal insulin therapy for the prevention of post-transplant diabetes onset after kidney transplantation), also corroborates the findings of the small non randomized study[50].

Dipeptidyl peptidase 4 (DPP-4) inhibitors have been shown to improve insulin sensitivity as well as β-cell function[51]. Vidagliptin, a DPP-4 inhibitor, has been shown to be safe and efficacious in kidney transplant patients[52] and a randomized trial is underway to test if vidagliptin could prevent PTDM development when used immediately post-transplant compared to placebo[53].

ii. Metformin

Metformin is still considered the first line therapy for DM treatment, but the association of metformin with lactic acidosis specifically in the setting of worsening kidney function complicates its use in post-transplant patients. Despite the risk of lactic acidosis, metformin can still be prescribed to patients with moderately reduced kidney function (glomerular filtration rate or GFR 30-59 mL/min)[54]. Metformin has minimal drug-drug interactions with immunosuppressant medications, but potentiation of metformin gastrointestinal (GI) side effects is possible when used concomitantly with mycophenolate mofetil (MMF). Close monitoring of kidney function is advisable during metformin therapy, in order to avoid potential treatment-related complications. In a small randomized trial that used metformin in patients that developed IGT 4-12 weeks post-transplant, metformin was well tolerated but did not show differences in metabolic profile compared to untreated patients[55]. Recent guidelines by the Association of British Clinical

Diabetologists (ABCD) and by the British Renal Association (RA) on the Detection and Management of Diabetes post-Solid Organ Transplantation continue to recommend metformin use if GFR allows it as one of the first line therapies in PTDM[56]. Further studies are needed to determine the efficacy of metformin in the prevention and management of PTDM.

iii. Sulfonylureas and glinides

Sulfonylureas and glinides stimulate pancreatic secretion of insulin independently of glucose levels. In contrast to glinides, most of the sulfonylureas significantly accumulate with kidney disease increasing the risk of hypoglycemia. Glinides are safer drugs in patients with kidney disease and more widely used post-transplantation. Unfortunately, despite frequent clinical utilization, there are only a few small studies that have tested these drugs in the setting of PTDM[57,58].

iv. Glucagon-like peptide 1 receptor agonists (GLP1-RAs)

GLP1-RAs improve glycemic control in T2DM through enhanced glucose-dependent insulin secretion, inhibition of glucagon release, delayed gastric emptying, appetite suppression, and inhibition of β-cell apoptosis[59]. Liraglutide, semaglutide and dulaglutide do not have significant kidney clearance, making them attractive agents in kidney transplant recipients. There is minimal data on liraglutide and dulaglutide safety after kidney transplantation[60-62]. In theory, GLP1-RAs may potentially exacerbate the frequent GI side effects seen with MMF due to their effect in delaying gastric emptying although this has not been observed in studies using dulaglutide.

v. Dipeptidyl peptidase 4 (DPP-4) inhibitors

DPP-4 inhibitors inactivate DPP4, the enzyme responsible for inactivation of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, thus enhancing glucose control. In contrast to GLP1-RAs, DPP-4 inhibitors have significant kidney clearance and dose reduction is necessary in patients with CKD.

Linagliptin is the only DPP-4 inhibitor that is non-renally cleared with predominant biliary clearance. DPP-4 inhibitors have some interactions with CNI metabolism as sitagliptin increases CSA levels and vidagliptin can decrease Tac trough levels. Linagliptin, sitagliptin and vidagliptin have been used in kidney transplant recipients with some benefits [52,63,64] and currently vidagliptin is being studied in a randomized controlled study for its use in the early post-operative period[53].

vi. Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2-i)

The two newest additions to the DM therapy armamentarium have been SGLT2-i and GLP1-RAs. SGLT2-i have received more attention recently as their use in diabetic patients is associated with lower cardiovascular disease risk and progression of CKD[65-69]. SGLT2-i selectively inhibit the sodium glucose co-transporter in the proximal convoluted tubule preventing glucose reabsorption. This mechanism of action results in a loss of significant amounts of glucose in the urine. Increased glycosuria facilitates urinary water losses which results in decreased blood pressure and weight loss, but also increases the risk of urinary tract infections and ketoacidosis.

SGLT2-i have shown evidence of reducing kidney disease progression in patients with T2DM[70-72] but trials in the PTDM population have been scarce. These benefits are independent of glucose control as the mean changes of HgA1c reported in clinical trials has been modest (around 0.5-0.6%)[66,67]. Recent published reviews of trials involving use of SGLT2-i in transplant recipients advocate for their widespread use[73,74] despite paucity of data. Currently, only a few observational and retrospective studies with SGLT2-i in a small number of transplant recipients[75-78] have been published and their main characteristics have been summarized in Table 2. Similarly to the diabetic trials in the non-transplant population, the efficacy of SGLT2-i in diabetic control is quite modest when used in patients with PTDM so most guidelines propose its use as an add on therapy[75-77,80,82]

Despite positive reviews, the main barrier to its widespread use in the transplant population has been the increased risk of bacterial and fungal infections of the genitourinary tract and perineum, including Fournier's gangrene, increased risk of amputations, and euglycemic acidosis. The increased risk of infections is thought to be related to the increased glucose content in the urine that makes a more favorable environment for bacterial growth. Transplant patients are inherently at higher risk for urinary tract and perineal infections due to immunosuppression and the physiological/anatomical changes that occur in the post-transplant genitourinary tract. Current trials that used SGLT2-i in transplant recipients have not demonstrated a higher risk of infection but data are limited due to small patient numbers. Other risks associated with SGLT2-i use include hemodynamic AKI due to afferent arteriole vasoconstriction coupled with volume loss due to its diuretic effect. None of these side effects have been reported in the trials that involved kidney transplant recipients, but most of the trials that used SGLT2-i post-transplant excluded patients with recurrent UTIs and patients within the first post-transplant year to minimize toxicity risk.

In summary, despite its modest anti-glycemic effects, SGLT2-i may confer similar cardiovascular and renal protection in kidney transplant recipients although further randomized control trials are needed to confirm this. SGLT2-i should be combined with other anti-diabetic agents but due to its potential for significant side effects, it seems prudent to limit its use to patients without a history of recurrent UTIs or perineal infections and avoid its use during the first post-transplant year. Caution should be used when given concomitantly with diuretics and antihypertensive medications due to potential changes in volume status. Consider holding SGLT2-i during acute illness to minimize the risk of diabetic ketoacidosis and vasomotor AKI.

c. Modification of immunosuppression

Immunosuppression is one of the most important modifiable risk factors for PTDM. Tailoring immunosuppression to patient risk for PTDM development is a logical step. Despite this, changes in immunosuppression agents during the first post-transplant year carries the risk of promoting rejection. It is well known that calcineurin inhibitors decrease insulin release from pancreatic β- cells and the use of Tac is associated with higher risk of PTDM compared to CSA[20]. Conversion from Tac based to CSA based immunosuppression in patients with PTDM was able to reverse diabetes mellitus in a significant number of patients[83]. Also, since the risk of PTDM is dose dependent, other studies have demonstrated a benefit on β-cell function with increased insulin secretion capacity once average Tac trough levels were decreased from 9.5 to 6.4 ng/mL[84]. The use of mTOR inhibitors is also associated with the development of PTDM[21] probably with lower risk than Tac but higher than CSA[85]. Some of the new immunosuppressant agents such as Belatacept have demonstrated metabolic benefits with higher insulin release and lower risk of PTDM development compared to Tac use[86] and this may be an interesting option that should be rigorously explored in clinical trials in subjects at high risk for PTDM. Antimetabolite use has not been demonstrated to increase PTDM risk. Despite the well-known role of steroids in the development of hyperglycemia and diabetes, the effect of steroids on the incidence of PTDM remains controversial. Several studies have shown that the risk of developing diabetes mellitus post-transplant is similar in patients that are maintained on steroids, versus patients that were not exposed to steroids or only exposed to steroids for a limited period of time[87-90]. On the other hand, rapid steroid withdrawal in a study from Germany showed significant reduction in the development of PTDM[91]. Transplant patients on 5 mg of prednisone demonstrated similar insulin sensitivity to patients not on steroid therapy[92]. Unfortunately, there is no data suggesting a benefit of immunosuppression adjustments without risk for increased rejection to prevent the development of PTDM and caution should be used when changes are made with the sole purpose of preventing diabetes.

d. Insulin pump treatment versus pancreas transplant for T1DM.

Intensive insulin therapy either with intermittent subcutaneous injections or by continuous subcutaneous delivery systems remains the cornerstone of therapy for patients with T1DM. Intensive insulin therapy has been demonstrated to decrease microvascular disease progression in patients with T1DM but, despite this, only a small proportion of patients meet the HgA1c goal set by the American Diabetes Association (ADA) in the T1D Registry[93,94] and most likely an even-smaller proportion of the general population[93]. The main barrier to achieve glucose control has been the risk of hypoglycemia. The technological advancements in insulin pumps, continuous glucose monitoring systems (CGMs) and artificial pancreas, where the capabilities of insulin pumps and CGMs are combined, have facilitated lower mortality, increased quality of life and decreased incidence of hypoglycemia[93,95,96]. Despite these new technologies, there are still multiple barriers to optimal glycemic control mainly related to their high cost and challenges in deployment for populations with disabilities. Pancreas transplantation provides the most durable replacement of β-cells in patients with insulin dependent diabetes. It is the most suitable therapy particularly in patients with advanced CKD as pancreas transplantation could be carried out concomitantly or after kidney transplantation. With a kidney transplant, the risk of long-standing immunosuppressive therapy is already accepted so there is less concern about the negative effects of immunosuppression. Pancreas transplantation not only improves quality of life but also has been demonstrated to decrease microvascular end organ damage[97]. With improvements in long term outcomes and decreased morbidity using current surgical techniques, pancreas transplantation is now available to a subset of insulin dependent[98] T2DM patients. In this subset, outcomes were excellent, with close to 90% of the patients being free of diabetes 5 years post-transplant. Pancreas transplantation without a kidney is mainly recommended for patients with T1DM with significant hypoglycemic unawareness despite CGMs or who are unable to achieve benefits of advance monitoring technologies. Patients should be free of CKD and proteinuria, as long-term use of immunosuppression will increase the risk of progressive kidney failure due to the nephrotoxicity of CNIs. Islet allotransplantation, where islet cells isolated from a donor are

injected into the portal vein of the recipient, is only available in specialized transplant centers. Less than 2000 islet cell transplants have been performed between 1999 and 2015 in North America. Islet transplantation is minimally invasive but still requires the use of immunosuppression. Recent trials have demonstrated that islet cell transplantation is safe, improves glycemic control, and quality of life[99]. Most of the patients will have resolution of hypoglycemic episodes and will improve glucose control with a secondary goal of achieving insulin independence at least in the short term. Long term insulin independence remains a challenge after islet cell transplantation[100]. Future therapies involve the use of embryonic stem cells or pluripotential stem cells, alternative transplant sites, use of other cell types besides β-cells in order to facilitate and prolong engraftment, or even gene editing to decrease cell immunogenicity and eliminate the need for ongoing immunosuppression. In summary, there are both medical and surgical options for T1DM treatment. These therapeutic options should be tailored to the unique circumstances of each patient at the specific moment of their disease course. Appropriateness of surgical and medical options may vary depending on the progression of diabetes during the patient's lifespan.

In summary, management of DM after transplantation remains a significant challenge as diagnosis can be obscured and treatment goals have not been fully delineated. Pharmacological therapies for DM have expanded significantly over the past few years but their role in improving outcomes in PTDM management is unknown. PTDM is an underexplored area within the metabolic disorders that affect kidney disease patients and should be the focus of future research.

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Table 1: Risk factors associated with the development of post-transplant diabetes mellitus

Factors unrelated to transplantation	Older age[101]
	Family history of DM
	Ethnicity Black and Hispanic
	Central obesity [102,103]
	Genetic factors[104]
	Sedentary lifestyle
Factors associated with transplantation	Calcineurin inhibitors (tacrolimus >cyclosporine) [20]
	Glucocorticoids[92]
	Hepatitis C or Cytomegalovirus infection[105,106]
	Post-transplant weight gain
	Hypomagnesemia[107]
	Inflammation and relative hypo-adiponectinemia[27,28,108]

Table 2. Summary of the studies using SGLT2-i in kidney transplant recipients.

Study reference	Study design	Agent	Population/Follow up	Key Findings
Rajasekeran H et al, 2017[76]	Case series, retrospective	Canagliflozin	10 kidney transplant and SPK recipients for 80.5 patient-months	Patients on canagliflozin had small decrease in HgA1c, small decrease in body weight, and a small decrease in GFR.
Mahling et al, 2019[77]	Case series, retrospective	Empagliflozin	10 kidney transplant recipients over 12 months	Patients on empagliflocin had stable GFR, and a small decrease in HbA1c.
Shah M et al, 2019 [78]	Case series, prospective	Canagliflozin	24 kidney transplant recipients over 6 months	Patients on canagliflozin had some weight loss, small reduction in BP and improvement of HgA1c
AlKindi F et al, 2020[75]	Case series, retrospective	Empagliflozin and dapagliflozin	8 living kidney transplant recipients over 3-6 months	Patients on SGLT2-i had stable GFR, small decrease in HgA1c, and small decrease in weight.
Halden et al, 2019[79]	Randomized, prospective, double blind	Empagliflozin vs placebo	44 kidney transplant recipient over 24 weeks	Empagliflozin use was associated with small changes in HbA1c and weight with no differences in adverse events
Schwaiger, E et al, 2019[80]	Prospective study	Empagliflozin	14 diabetic kidney transplant participants	Empagliflozin may be used as add-on therapy for treatment of diabetes after transplant.
Song CC et al, 2021[81]	Retrospective study	Empagliflozin, canagliflozin and dapagliflozin.	50 kidney transplant participants over 6 months	Patients on SGLT1-i had decrease weight and increase magnesium concentration.

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