DIABETES MELLITUS AFTER SOLID ORGAN TRANSPLANTATION

Phuong-Thu Pham, MD, Professor of Medicine, David Geffen School of Medicine at UCLA, Department of Medicine, Nephrology Division, Kidney Transplant Program, Los Angeles, CA 90095. PPham@mednet.ucla.edu
Mrinalini Sarkar, **MD,** Clinical Instructor, David Geffen School of Medicine at UCLA, Department of Medicine, Nephrology Division, Kidney Transplant Program, Los Angeles, CA 90095. MSarkar@mednet.ucla.edu
Phuong-Mai Pham, MD, Professor of Medicine, VA Greater Los Angeles Health Care System, Department of Medicine, North Hills, CA 91343. Phuong-mai.pham@va.gov
Phuong-Chi Pham, MD, Professor of Medicine, Olive View-UCLA Medical Center, Department of Medicine, Nephrology Division, Sylmar, CA 91345. pctp@ucla.edu

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ABSTRACT

Post transplantation diabetes mellitus (PTDM), also known as New Onset Diabetes After Transplantation, is a common and important complication following solid organ transplantation. PTDM may arise from both transplant-related and traditional risk factors and has variably been reported to be associated with decreased patient and graft survival and other adverse outcomes including increased cardiovascular disease risk, infection, and graft rejection. This chapter reviews the nomenclature change for post-transplant diabetes, diagnostic criteria, risk factors, incidence after solid organ transplantation, and associated adverse effects. Screening for PTDM including pretransplant evaluation and early detection in the posttransplant period, and the unique aspects of diabetes management in the context of organ transplantation are also discussed.

NOMENCLATURES AND DIAGNOSIS OF POSTTRANSPLANTATION DIABETES MELLITUS: HISTORICAL PERSPECTIVES

Nomenclatures

Post transplantation diabetes mellitus (PTDM) was first described in kidney transplant recipients in 1964 (1). It was subsequently recognized as a complication of kidney transplantation in the 1970s. Over the years, PTDM has undergone changes in nomenclatures including steroid diabetes, post transplantation diabetes mellitus (PTDM), new onset diabetes mellitus (NODM), transplant-associated hyperglycemia (TAH), and new onset diabetes after transplantation (NODAT) (2, 3, 4, 5, 6). In 2014, the International Expert Panel consisting of transplant nephrologists, diabetologists, and clinical scientists recommended changing the terminology NODAT back to PTDM, excluding transient post transplantation hyperglycemia (7). Utilizing the term NODAT is thought to be misleading because it seemingly excludes patients with pretransplant diabetes. Pre-existing diabetes is often undiagnosed because of the effect of chronic kidney disease on insulin metabolism and clearance, and the lack of effective pretransplant screening. The term PTDM will be utilized for the remainder of this chapter.

Diagnosis

Historically, PTDM has been variably defined as having random glucose levels greater than 200 mg/dL, fasting glucose levels greater than 140 mg/dL, or the need for insulin or oral hypoglycemic agents in the posttransplant period (8). In 2003 the International Expert panel consisting of leaders from both the transplant and diabetes fields suggested that the definition and diagnosis of diabetes and impaired glucose tolerance should be based on the definition and diagnosis described by the World Health Organizations (9). In 2011, the American Diabetes Association (ADA) incorporated hemoglobin A1C (A1C) > 6.5% as a diagnostic criterion for diabetes mellitus in the

general population based on the observed association between A1C level and the risk for future development of retinopathy (10). In 2014, the International Expert Panel recommended expanding screening tests for PTDM using postprandial glucose monitoring and A1C. However, A1C test is not recommended early after transplantation (arbitrarily defined as within 45 days after transplantation) because of potential confounding factors (7). A normal A1C does not exclude the diagnosis of PTDM in the presence of early posttransplant anemia and/or dynamic kidney allograft function. In a small single-center study consisting of 30 diabetic patients with CKD stage 3 b and 4, treatment with intravenous iron and erythropoietin stimulating agent (ESA) has been shown to result in a fall in A1C independent of glycemic changes (11). It is speculated that the fall in A1C level associated with either treatment is due to the formation of new erythrocytes in the circulation (causing a change in the proportion of young to old red blood cells), and an alteration in the red-cell glycation rates. A similar study in the transplant setting is lacking and warrants further exploration because intravenous iron and ESA therapy are commonly administered in the early posttransplant period. Although not widely used in clinical practice, oral glucose tolerance (OGTT) remains the gold standard for diagnosing PTDM. It should be noted that the algorithmic approach to the screening and diagnosis of PTDM is largely based on published kidney transplantation literature. Similar studies in the settings of liver, heart, and lung transplants are lacking. However, it is speculated that the principles are relevant to all forms of solid organ transplantation (7). The 2022 ADA criteria for prediabetes and diabetes are shown in Figure 1.

Test	Prediabetes[1]	Diabetes[2]	Comments
A1C	A1C 5.7-6.4%	≥ 6.5%	A1C should be measured in a NGSP-certified laboratory. The purpose of the NGSP is to standardize HbA1c test results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which established the direct relationships between A1c levels and outcome risks in patients with diabetes.
Fasting plasma glucose (FPG)	100-125 mg/dL (5.6-6.9 mmol/L)	≥ 126 mg/dL (7.0 mmol/L)	No caloric intake for at least 8 hours
2-h plasma glucose during OGTT	140-199 mg/dL (7.8-11.1 mmol/ L)	≥ 200 mg/dL (11.1 mmol/L)	Using glucose load of 75 g anhydrous glucose dissolved in water
Random plasma glucose[3]		> 200 mg/dL (11.1 mmol/L)	Random glucose: Any time of the day without regard to time since last meal Symptoms: Polyuria, polydipsia, unexplained weight loss

Figure 1. The 2022 American Diabetes Association Diagnostic Criteria for Prediabetes and Diabetes.
[1]For A1C, FPG and 2-h OGTT, risk is continuous, extending below the lower limit of the range, becoming disproportionately greater at the higher end of the range. [2]In the absence of unequivocal hyperglycemia, diagnosis of DM using A1C, FPG or 2-h OGTT requires two abnormal test results from the same sample or in two separate samples. [3]Random plasma glucose is only diagnostic in patient with classic symptoms of hyperglycemia or hyperglycemic crisis (https://doi.org/10.2337/cd22-as01). OGTT, oral glucose tolerance test; A1C, hemoglobin A1C; NGSP, National Glycohemoglobin Standardization Program

INCIDENCE

PTDM has been reported to occur in 4% to 25% of kidney transplant recipients, 2.5% to 25% of liver transplant recipients, 4% to 40% of heart transplant recipients, and 30% to 35% of lung transplant recipients (9, 12-15). Higher incidences have also been reported. Variations in the reported incidence may be due in part to the prior lack of a standard definition, presence of both modifiable and nonmodifiable risks factors, duration of follow-up, type of organ transplants, and primary diagnostic indications for transplant. In one retrospective cohort study of 415 liver transplant recipients, PTDM occurred in 34.7%, 46.9%, and 56.2% of patients at 1, 3, and 5-year follow-up, respectively (15). The 33rd International Society of Heart and Lung Transplantation database demonstrated that approximately 29% of lung transplant recipients who survived 5 years post-transplantation developed PTDM, with the highest incidence occurring among those whose primary diagnosis for lung transplantation was cystic fibrosis. (16).

RISK FACTORS FOR PTDM

PTDM may arise from both transplant-related and traditional risk factors. The diabetogenic effect of various immunosuppressive agents have been well described. Corticosteroids may reduce peripheral insulin sensitivity, inhibit pancreatic production/secretion, and increase hepatic gluconeogenesis. The calcineurin inhibitors tacrolimus and cyclosporine decrease insulin secretion and synthesis. Sirolimus increases peripheral insulin resistance and impairs pancreatic beta-cell response. The antimetabolites azathioprine and mycophenolic acid derivatives (mycophenolate mofetil and mycophenolate sodium) are not diabetogenic. Belatacept is a humanized fusion protein that inhibits the costimulatory pathway. Its use in kidney transplant recipients has not been shown to increase PTDM risk. Transplant patients may have improved appetite and a more liberal diet which can lead to obesity. Risk factors for PTDM can be loosely categorized into those that are non-modifiable, potentially modifiable, and modifiable (8, 17-24).

Solid organ transplant recipients with specific end-organ diagnosis such as end-stage kidney disease due to polycystic kidney disease, end-stage lung disease due to cystic fibrosis, or end-stage liver disease due to hepatitis C infection or nonalcoholic steatohepatitis have been reported to be at increased risk for PTDM compared with those without such diagnosis (21). Donor liver steatosis has also been reported to be associated with an increased incidence of PTDM (22). Suggested risk factors for the development of PTDM are presented in Figure 2. A more extensive discussion of the studies evaluating PTDM risk factors is beyond the scope of this chapter. Interested readers are referred to reference Pham and colleagues (8).

Non-modifiable	Potentially modifiable	Modifiable[4]	End-organ specific diagnosis
African American, Hispanic Age > 45 years Male recipient Family history of diabetes mellitus Human Leukocyte Antigen (HLA) mismatches HLA A30, B27, B42 Acute rejection history Deceased donor Male donor Genetic polymorphism [e.g. TCF7L2 variant (rs7903146), PPAR-α variant (rs4253728), HNF-4A, insulin receptor substrate-1]	Hepatitis C virus[1] Cytomegalovirus[2] Pretransplant IGT/IFG Proteinuria Hypomagnesemia[3]	Obesity (body mass index ≥ 30) LDL cholesterol Steroids, tacrolimus, cyclosporine, sirolimus Vitamin D deficiency	End stage kidney disease due to polycystic kidney disease End stage liver disease due to HCV infection or non-alcoholic steatohepatitis (NASH)[5] End stage lung disease due to cystic fibrosis

Figure 2. Suggested Risk factors for PTDM

[1]Curative therapy for chronic hepatitis C can be achieved with interferon-free direct acting antiviral-based regimen. Stable transplant recipients with HCV viremia by PCR should be referred to Hepatology for treatment. In HCV-positive kidney transplant candidate with a living donor, pretransplant treatment of HCV infection should be considered. [2]Posttransplantation CMV prophylaxis is preferred over preemptive therapy after heart and lung transplant. Either prophylaxis or preemptive therapy is recommended after kidney or liver transplant recipients. However, for programs or patients who are unable to meet the stringent logistic requirements required with preemptive therapy, prophylaxis therapy is recommended. [3]Persistent hypomagnesemia can occasionally be seen despite aggressive replacement therapy because of ongoing calcineurin inhibitor-induced urinary magnesium wasting. [4]Manipulation of immunosuppression should be weighed against the risk of acute rejection. [5]Donor liver steatosis has also been reported to be associated with increased PTDM risk. PPAR, peroxisome proliferators activated receptor; IGT, impaired glucose tolerance; IFG, impaired fasting glucose

IMPACT OF PTDM ON OUTCOMES AFTER TRANSPLANTATION

Studies evaluating the association between PTDM and morbidity and mortality have yielded mixed results (25-33).

PTDM After Kidney Transplantation

Retrospective analysis of the United States Renal Data System consisting of more than 11,000 kidney transplant recipients demonstrated that PTDM was a strong, independent predictor of mortality ($p < 0.0001$), graft failure (unadjusted for graft loss due to rejection) ($p < 0.0001$), and death-censored graft failure ($p < 0.0001$) (18). One single-center study consisting of more than 700 kidney transplant recipients similarly demonstrated worse 10-year actuarial patient survival among patients with PTDM compared with those without PTDM (67.1% vs. 81.9%, respectively). Five- and 10-year graft survival rates were similar among patients with PTDM and those without

PTDM (25). In contrast, in a multicenter longitudinal cohort study consisting of 632 kidney transplant recipients of deceased-donor kidneys, no association between PTDM and mortality or graft failure was observed at a median follow-up of 6 years post-transplantation (n=632) (26). Subgroup analyses showed that late onset PTDM (developing beyond 1-year post-transplantation) was associated with worse graft outcomes. A retrospective analysis of the UNOS/OPTN database (n > 37,000) similarly failed to demonstrate the negative impact of PTDM on transplant survival or cardiovascular mortality during a median follow up of 548 days (27). However, the study results were considered inconclusive because of the wide confidence intervals and relatively short duration of follow-up.

PTDM After Liver Transplantation

Retrospective analysis of the UNOS/OPTN database consisting of > 13,000 liver transplant recipients demonstrated that the presence of both PTDM and acute rejection at 1-year posttransplant but not PTDM alone was associated with higher overall graft failure and mortality risk (27). However, it should be noted that UNOS database did not distinguish transient post transplantation hyperglycemia from established PTDM. A single-center retrospective cohort study (n=994) compared the incidence of major cardiovascular events (MCE) among four groups of liver transplant recipients 1) without diabetes (39%), 2) with pre-existing diabetes (24%), 3) with transient PTDM (16%), and 4) with sustained PTDM (20%). Sustained PTDM was found to be associated with a significant increase in mortality risk and a doubling of major cardiovascular events at a median follow up of 54.7 months (sub-distribution HR 1.95, 95% CI 1.20–3.18). A greater than threefold increased risk of death was observed among those who experienced MCE (sustained PTDM was defined as PTDM for at least 6 months after transplant). MCE was defined as a composite of cardiac arrest, fatal and nonfatal myocardial infarction, ischemic stroke, and symptomatic peripheral artery disease requiring a revascularization intervention) (30). In a retrospective cohort study of 415 adult liver transplant recipients, PTDM was found to be associated with higher rejection rates (31.9% vs. 21.8%, respectively; p=0.055) and a trend towards worse patient survival compared with no-PTDM at 5 year follow up (72.5% vs. 77.2%, respectively; p=0.460) (15). Although studies on the association between PTDM and patient and allograft outcomes after liver transplantation have yielded variable results, most studies demonstrated that PTDM after liver transplantation is associated with increased mortality risk (31).

PTDM After Heart Transplantation

Meta-analysis of observational studies in heart transplant recipients demonstrated that pre-existing diabetes was associated with a 37% increase in mortality risk (HR 1.37, CI 1.15-1.62) (32). Studies on the impact of PTDM on outcomes after heart transplantation are lacking. In one single-center South Korean study consisting of 391 isolated heart transplant recipients 1) without diabetes (n=257), 2) with pre-existing diabetes (n=46), and 3) with PTDM (n=88), the risk of death was found to be twofold higher among transplant recipients with pre-existing as well as post transplantation diabetes compared with their non-diabetic counterparts (33).

PTDM After Lung Transplantation

The 27th International Society for Heart and Lung Transplantation Registry consisting of more than 32,000 lung transplant recipients demonstrated that pre-existing diabetes was associated with a 21% increase in 5-year mortality risk (RR 1.21, p=0.0023) (34). Limited studies suggest that PTDM similarly adversely affects survival among lung transplant recipients. In a single-center prospective observational Australian study consisting of 210 patients who underwent their first single, bilateral, or heart-lung transplant between 2010-2013, hyperglycemia in both the early and late posttransplant periods (defined as first 4 months and beyond 4 months) was found to be associated with increased mortality risk. Of 210 patients, 80 had no DM, and 90 had persistent DM. Patients with preexisting DM (n=45) and PTDM (n=45) were classified together as “persistent DM”. In the whole cohort, each 18 mg/dL increase in mean fasting blood glucose (FBG) and random blood glucose and each 1% increase in mean A1C were associated with 18% (p=0.006), 38% (p< 0.001), and 46% (p=0.002) increase in mortality risk, respectively (median follow up of 3 years). Of interest, random blood glucose correlated with mortality in both the persistent DM and no DM groups (35%, p=0.012 and 109%, p=0.041,

respectively). It was concluded that glycemic control strongly correlated with survival after lung transplant (35). The same group of investigators previously demonstrated that DM conferred a nearly fourfold increase in mortality risk compared with no DM. When patients were classified into subgroups including 1) no diabetes, 2) pre-existing DM, 3) PTDM, 4) DM diagnosed within 2 weeks of death, and 5) DM developing after transplant but death within 90 days of transplant, pre-existing DM and PTDM were associated with a 65% ($p=0.003$) and a 90% ($p<0.001$) increase in mortality risk, respectively (36).

Although studies on the impact of PTDM on outcomes after non-renal solid organ transplantation remain limited, PTDM appears to be associated with increased mortality risk regardless of the type of organ transplants (kidney, liver, heart, lung transplant) (21). Patients with PTDM may also develop many of the complications associated with diabetes similar to that observed in the general population. In a study of 4105 patients with PTDM, one or more diabetic complications arose in 58% including ketoacidosis (8%), hyperosmolarity (3%), renal complications (31%), ophthalmic complications (8%), neurological complications (16%), peripheral circulatory disorders (4%), and hypoglycemia/shock (7%). These complications occurred within a mean of 500-600 days of developing PTDM, indicating an accelerated pace for the development of complications (28). Moreover, PTDM patients had an increased rate of infections and sepsis compared with their non-diabetic counterparts.

DETECTION OF PTDM

Pretransplant Baseline Evaluation

Pretransplant Evaluation should include history of hyperglycemia, prediabetes, diabetes, and risk factors for PTDM including family history and hepatitis C virus. The 2004 International Consensus Guidelines suggest that a pretransplant baseline evaluation should include a complete medical and family history, including documentation of glucose history (37). Those with risk factors for metabolic syndrome can be screened further with laboratory testing. Patients with evidence of risk factors can be counseled of their risk for PTDM. Those with evidence of prediabetes can be counseled on lifestyle modifications including dietary modifications, thirty minutes of moderate intensity physical activity, and overall five to ten percent weight reduction (38). In HCV-positive kidney transplant candidates with a living donor, pretransplant treatment of HCV infection should be considered. With the advent of the interferon-free direct acting antiviral based regimen, treatment of hepatitis C in the posttransplant period is a reasonable alternative in selected prospective kidney transplant candidates without a living donor due to a considerably shorter waiting time for a deceased HCV-positive donor kidney (39). The choice of an immunosuppressive regimen should be tailored to each individual patient, weighing the risk of acute rejection against that for PTDM.

Early Detection of PTDM After Transplantation

New onset perioperative hyperglycemia is common and may develop in the context of high dose corticosteroid, as a consequence of posttransplant stress hyperglycemia, or both. Limited studies suggest that posttransplant stress hyperglycemia is an independent risk factor for subsequent diabetes (40). The 2014 International Consensus guidelines on PTDM screening is shown in Figure 3 (7). The expert panel suggested that patients with early post-transplant hyperglycemia (defined as hyperglycemia before 45 days after transplantation) should not be diagnosed as PTDM.

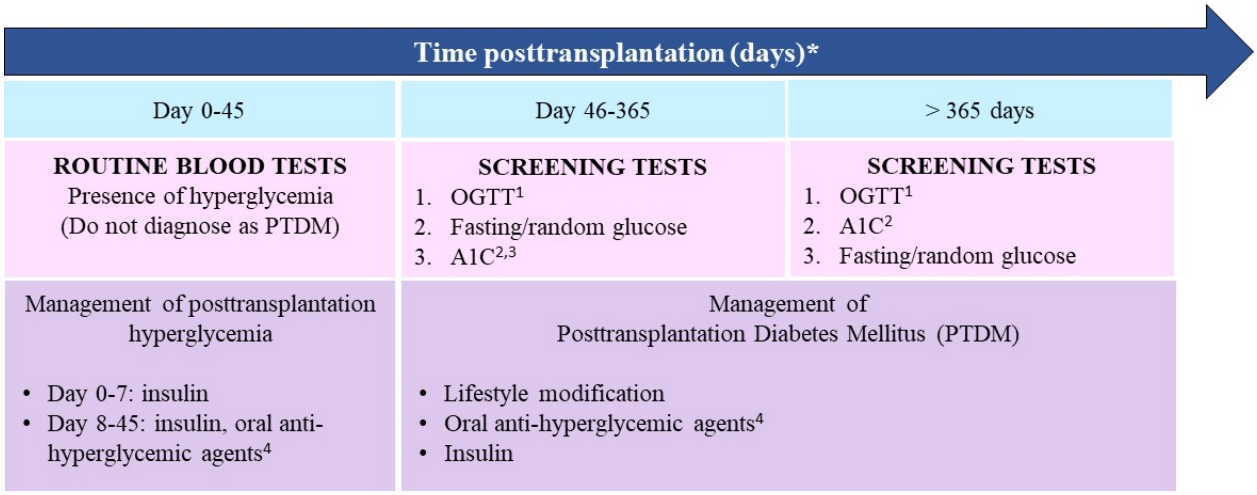

Figure 3. The 2014 International Consensus Guidelines on Screening, Diagnosis, and Management of PTDM
[1]Seldom performed in clinical practice (time-consuming/cost). [2] A1C cannot be accurately interpreted within the first 3 months after transplantation because anemia and impaired graft function can directly interfere with the A1C assay. Recent blood transfusion and dapsone may alter A1C level. [3]A1C alone < 365 days may underestimate PTDM and require confirmatory testing. [4]Within the past several years newer injectable antidiabetic agents have increasingly been used (however, it should also be noted that evidenced-based recommendations are lacking). PTDM, post-transplantation diabetes mellitus; OGTT, oral glucose tolerance test; A1C, hemoglobin A1C

At the authors' institution, fasting and premeal home glucose monitoring is routinely recommended for patients with new-onset post transplantation hyperglycemia particularly those requiring insulin therapy in the immediate post transplantation period. Nonetheless, it should be noted that monitoring a 2- hour postprandial blood glucose may be a better indicator of diabetes, particularly in steroid-treated patients. Clinically stable patients with persistent post transplantation hyperglycemia for > 3 months should be screened for PTDM using A1C test. Although evidence-based screening guidelines for the early detection of PTDM are lacking, obtaining baseline A1C at 3 months after transplant, then at 6 months, 9 months, 12 months, and annually thereafter seems reasonable. If screening A1C is in the prediabetic range, patients should be counseled on dietary and lifestyle modification and A1C monitored every 3 months. While OGTT remains the gold standard for diagnosing PTDM, there remains insufficient evidence to recommend OGTT for all kidney transplant recipients (7). In addition, screening all patients with OGTT may be impractical in clinical practice and should be individualized and reserved for those with multiple risk factors (opinion-based) (40,41).

PREVENTION AND MANAGEMENT OF PTDM

Non-Pharmacological Preventive and Management Strategies

Studies in the general population demonstrated that lifestyle modification promoting reduced fat/energy diet, daily moderate intensity physical activity, and modest weight loss reduce the incidence of type 2 diabetes (42). Similar studies in the context of solid organ transplantation are limited. Small single-center studies showed that post transplantation weight gain is associated with persistent PTDM (43). In a small single center study consisting of 25 kidney transplant recipients with impaired glucose tolerance, reversal to normal glucose tolerance with lifestyle modification was observed in 13 patients after a median of 9 months with only one patient progressing to PTDM (44). In contrast, a single-center, randomized controlled trial designed to Compare the benefits of Active Versus passive lifestyle Intervention in kidney Allograft Recipients (CAVIAR) showed no improvement in surrogate markers of glucose metabolism (insulin secretion, insulin sensitivity, and disposition index) among patients randomized to active lifestyle intervention (lifestyle change

with the guidance of a renal dietitian, n=66) compared with their passive lifestyle intervention counterparts at 6 month follow-up (leaflet advice alone, n=64). However, clinically, active versus passive lifestyle intervention resulted in weight loss (-2.47 kg, P=0.002) and reduction in fat mass (mean difference, -1.537 kg, P=0.123). A trend towards reduction in PTDM incidence (7.6% versus 15.6%, P = 0.123) was observed in the active intervention arm (45).

Pharmacological Preventive and Management Strategies

In the immediate posttransplant period, the pancreatic β-cells are exposed to multiple hyperglycemic stressors including the transplant surgery itself, high-dose corticosteroids, and the introduction of cyclosporine or tacrolimus immunosuppression therapy. It has been suggested that early basal insulin therapy decreases PTDM through insulin-mediated protection of pancreatic beta-cells (46-47). In a randomized controlled trial, Hecking *et al.* demonstrated that early basal insulin therapy following detection of early post transplantation hyperglycemia (defined as < 3 weeks) reduced the subsequent odds of developing PTDM within the first year after transplantation by 73% (47). In an open-label, multicenter randomized trial comparing early post-operative basal insulin therapy vs. standard of care for the prevention of PTDM in kidney transplant recipients, early insulin therapy was similarly found to result in reduced odds for PTDM at 12 months (OR: 0.21 [95% CI, 0.07 to 0.62]) and at 24 months (OR 0.35 [95% CI, 0.14 to 0.87]) after adjustment for baseline differences including polycystic kidney disease. However, treatment resulted in significantly higher hypoglycemia rates (48). Currently, initiation of insulin therapy in the early post-transplantation period solely to prevent PTDM cannot be routinely recommended and awaits further study. The glucose threshold for starting insulin therapy remains to be defined. Insulin tapering or withdrawal and transitioning to noninsulin-based regimen can be considered after the first 1-3 month after transplant when insulin requirement is less than 15-20 units a day (opinion-based). The choice of individual agents should be based on the potential advantages and disadvantages of different classes of agents at the discretion of the clinicians (Figure 4).

Agents	Advantages	Disadvantages/Comments
Insulin Sensitizers		
Biguanides Examples: metformin[1], buformin	Weight neutral or weight loss, no hypoglycemia, cardioprotection (metformin)	Gastrointestinal intolerance, lactic acidosis with renal impairment[1]
Thiazolidinedione derivatives Examples: pioglitazone	Low hypoglycemic risk, does not depend on renal excretion	Fluid retention: worsen CHF (not recommended following heart transplantation), edema (especially with insulin), weight gain, accelerated bone loss, increase fracture risk Contraindicated in NYHA functional classes III-IV CHF or hepatic impairment
Insulin Secretagogues		
Sulfonylureas Examples: glipizide, glyburide		Weight gain, edema, hypoglycemia (particularly in elderly and patients with renal impairment) Glyburide may accumulate in renal insufficiency SMZ-TMP coadministration increases hypoglycemia risk[2]
Glinides Examples: repaglinide, nateglinide	Glinides: rapid onset and offset. Best suited for patients whose food intake is erratic (best taken before meals, and the dose may be omitted if a meal is skipped)	Weight gain, hypoglycemia (lower risk than sulfonylureas)
Glucagon-Like Peptide-I Analogues		
Examples: dulaglutide, liraglutide, exenatide (renal dosing)	Weight loss (delayed gastric emptying, early satiety), low risk of hypoglycemia	GI intolerance Risk of pancreatitis Medullary thyroid cancer[3] (FDA black box warning)
Dipeptidyl Peptidase-4 inhibitors		
Examples: vildagliptin, sitagliptin,[4] linagliptin	Weight neutral, low risk for hypoglycemia Possible β-cell preservation	Renal dosing except linagliptin (clinicians should refer to package inserts) Risk of pancreatitis, ketoacidosis Saxagliptin and alogliptin (FDA warning of potential increased heart failure risk)
Sodium-glucose cotransporter type 2 (SGLT2) inhibitors		
Examples: empagliflozin, canagliflozin, dapagliflozin,	Cardio- and reno- protection Weight loss Blood pressure lowering Lower serum uric acid level Increase hemoglobin/hematocrit Increase serum magnesium level (beneficial in CNI-induced hypomagnesemia)	Increased risk for UTIs, genital candidiasis, euglycemic DKA, acute kidney injury Increase LDL level Contraindications: Type 1 DM, history of DKA or euglycemic DKA, chronic hypotension or recurrent volume depletion

Figure 4. The potential advantages and disadvantages of various classes of antihyperglycemic agents.
[1] KDIGO guidelines: Reduce dose if estimated glomerular filtration rate (eGFR) < 45 cc/min/1.73 m^2. Discontinue if eGFR < 30 cc/min/1.73m^2. [2] From Parekh TM, Raji M, Lin YL, et al. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. JAMA Intern Med. 2014;174(10):1605-1612. [3] Contraindicated

in patients with personal history or family history of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2. [4] Sitagliptin may prolong QT interval particularly when used with cyclosporine.

Modification of Immunosuppression

Although clinical trials comparing the incidence of PTDM in cyclosporine versus tacrolimus-treated patients have yielded variable results, tacrolimus has more consistently been shown to have a greater diabetogenic effect than cyclosporine (49). Modification of immunosuppression including cyclosporine to tacrolimus conversion therapy or steroid avoidance, or withdrawal has variably been shown to improve glycemic control (8, 49-53). However, manipulation of immunosuppression is not without immunological risk. In a meta-analysis of controlled clinical trials to assess the safety and efficacy of early steroid withdrawal or avoidance, Pascual *et al.* showed that steroid avoidance or steroid withdrawal after a few days reduced PTDM incidence among cyclosporine but not tacrolimus-treated kidney transplant recipients (54). However, among cyclosporine-treated patients, acute rejection episodes were more frequently observed in steroid avoidance compared with conventional steroid treated groups. The same group of investigators demonstrated no significant beneficial effect of late steroid withdrawal (3 to 6 months after transplantation) on the incidence of PTDM (55). In the current era of immunosuppression, the beneficial effect of steroid avoidance or withdrawal on the incidence of PTDM has been questioned by experts in the field because rapid steroid taper and the use of lower target cyclosporine and tacrolimus levels are now common practice (7). The use of tacrolimus and mTOR inhibitor combination therapy may increase PTDM risk and should probably be avoided. Nonetheless, low dose calcineurin inhibitor (cyclosporine or tacrolimus) and mTOR inhibitor combination therapy seems justifiable in transplant recipients with a history of malignancies (such as skin cancers, renal cell carcinoma, or Kaposi sarcoma). Due to the lack of well-defined guidelines, modification of immunosuppression to alleviate the incidence of PTDM should be tailored to each individual patient. Reduction in immunosuppression should be weighed against the risk of acute rejection.

Management of Established PTDM in the Late Posttransplant Period

Although there may be differences in the pathogenesis and presentation of PTDM compared to type 2 diabetes mellitus, management of established PTDM in the late posttransplant period should follow the conventional approach and clinical guidelines as established by well-recognized organizations. The American Diabetes Association and European Association for the Study of Diabetes generally recommend an A1c target of < 7% (56). Lower A1C levels may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other treatment-related adverse effects. In contrast, less stringent A1C goals may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits (57). Lifestyle modifications including weight reduction, dietary changes, and regular moderate cardiovascular activity should be employed. If glycemic control does not reach therapeutic targets, medical management with antidiabetic agents and ultimately insulin can be initiated.

Metformin has not been widely used in the setting of transplantation due to the concern for lactic acidosis in the presence of dynamic kidney allograft function particularly in the early post transplantation period. In contrast, the potential beneficial effects of metformin including weight neutral or weight loss, cardio protection, and lack of significant drug-drug interactions renders metformin an attractive treatment option for solid organ transplant recipients. There has been only one randomized clinical trial assessing the efficacy of metformin in the prevention of PTDM in kidney transplant recipients –The Transplantation and Diabetes (Transdiab) study (58). The Transdiab study is a single-center, open label, randomized controlled trial designed to assess the feasibility, gastrointestinal tolerability, and efficacy of metformin in patients with post transplantation impaired glucose tolerance. The latter is diagnosed using a 2-hour oral glucose tolerance test in the 4-12 weeks after transplant. Patients with eGFR < 30 mL/min/1.73 m^2 were excluded from the study. Eligible patients with IFG were randomized to standard of care (n=9) or standard of care and metformin 500 mg twice daily (n=10). The efficacy of metformin was assessed by measuring fasting blood glucose and A1C at 3, 6, 9, and 12-month follow up. The

study demonstrated similar tolerability and efficacy between the two groups. The former was evaluated by the gastrointestinal symptom rating scale at 3- and 12-months post randomization. At 12-month follow-up, 60% of patients in the metformin arm and 22% in the control arm returned to a normal OGGT (P=0.2). Both groups gained weight by the end of 12 months with the intervention group gaining 2.2 kg and the control group 6.7 kg (P=0.12). One patient discontinued metformin due to gastrointestinal symptoms and another patient required metformin dose reduction due to a metallic taste. One patient in the control group was started on metformin 500 mg twice daily by the treating physician 6 months after randomization due to elevated FBG and A1C. There were no episodes of lactic acidosis or serious adverse events in either arm. Although large randomized controlled trials to assess the risk and benefit ratio of metformin are needed before it can be endorsed as the oral antidiabetic agent of choice in PTDM, its use appears safe in kidney transplant recipients with mild to moderate renal impairment (eGFR 30-60 mL/min).

Experimental studies suggest that sulfonylureas are associated with β-cell apoptosis and β-cell exhaustion (59), raising theoretical concern about their use in PTDM, particularly in the early posttransplant period. In contrast, the anti-hyperglycemic dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitors have been shown to preserve pancreatic beta-cell function in diabetic animal models (60-61).

Early clinical studies suggest that DPP-4 inhibitors are safe and effective in the treatment of PTDM in kidney transplant recipients (62-64). In a single-center study consisting of 71 stable kidney transplant recipients with PTDM newly diagnosed by an oral glucose tolerance test, Haidinger *et al.* demonstrated that patients treated with vildagliptin at baseline had significantly reduced HbA1C levels at 3, 6,12, and 18 months, whereas no improvement in glycemic control was observed among their sulfonylurea-treated counterparts (62). In a randomized controlled trial comparing vildagliptin with placebo in the treatment of PTDM, the same group of investigators demonstrated that treatment with vildagliptin significantly improved A1C levels within 3 months compared with placebo (65). In a systematic review and meta-analysis to assess the efficacy and safety of DDP-4 inhibitors in kidney transplant recipients with PTDM, DDP4-inhibitor use was found to have a favorable glycemic effect (assessed by A1C) compared with either placebo or oral anti-hyperglycemic agent (A1C= -0.993, p=0.001) at 6-month follow-up. No significant changes in eGFR or tacrolimus levels were observed in DDP-4 inhibitor-treated patients (66).

Studies evaluating the safety and efficacy of DDP-4 inhibitors in non-renal solid organ transplant recipients remain lacking. In a small retrospective study of 30 stable heart transplant recipients with type 2 diabetes, vildagliptin was found to significantly reduce A1C level compared with their control counterparts. Mean A1C in the vildagliptin-treated patients was 7.4% ± 0.7% before versus 6.8% ± 0.8% after 8 months of therapy (P = 0.002 vs baseline). Mean A1C levels at baseline and at 8-month follow up in the control group were 7.0% ± 0.7% versus 7.3% ± 1.2%, respectively (P = 0.21) (67). No statistically significant changes in body weight, total cholesterol or triglyceride levels were seen in vildagliptin-treated patients. Furthermore, no significant changes in immunosuppressive drug levels or dosages were observed in either group. Whether vildagliptin is safe and effective in the treatment of PTDM after orthotopic heart transplantation warrants further exploration. In contrast, in a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the long-term cardiovascular efficacy and safety of saxagliptin in patients with type 2 DM at risk of cardiovascular events, saxagliptin administration was unexpectedly found to be associated with a significant 27% increase in hospitalizations for heart failure [the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, n =16,492) (68). However, subsequent *post-hoc* analyses of two large randomized placebo-controlled trials (EXAMINE and TECOS trials) showed no increase in heart failure risk in alogliptin- (69) or sitagliptin-treated patients (70) compared with their placebo-treated counterparts, suggesting that the increase in heart failure incidence observed with saxagliptin may be specific to the drug rather than a drug class effect. Nonetheless, based on early clinical study results, the FDA has issued a warning about the potential for increased risk for heart failure associated with the use of saxagliptin and alogliptin. Saxagliptin use in recipients of heart transplantation with

PTDM is not recommended. Whether alogliptin is safe for use after heart transplantation awaits further studies.

GLP-1 agonists therapy may confer cardioprotective (liraglutide, dulaglutide, and semaglutide) and weight-loss benefits, counteracting the weight gain commonly seen in the setting of hyperglycemia and steroid therapy after transplantation (16, 71-72)

The novel sodium-glucose cotransporter type 2 inhibitor (SGLT2i) antidiabetic drug class inhibits glucose reabsorption in the proximal convoluted tubule resulting in glucosuria. The glucosuric effect of SGLT2i is attenuated in patients without hyperglycemia thereby lessening hypoglycemia risk. An experimental animal model of tacrolimus-induced diabetes demonstrated that empagliflozin improves hyperglycemia and suppressed the tacrolimus-induced twofold increase in the expression of SGLT2 receptors (73). Furthermore, empagliflozin was found to have a direct protective effect on tacrolimus-induced renal injury. The study findings suggest that SGLT2 inhibitor is a suitable therapeutic option for transplant recipients with tacrolimus induced PTDM.

Although initially approved for use as an antidiabetic agent, SGLT2i use was unexpectedly found to have cardio- and reno-protective effects in subjects with or without type 2 DM (74-76). The EMPEROR-Reduced randomized placebo-controlled trial designed to study the effect of empagliflozin on cardiovascular and kidney outcomes across the spectrum of kidney function demonstrated a significant reduction in cardiovascular death, heart failure hospitalization, and total heart failure hospitalization among empagliflozin-treated patients compared with their placebo-treated counterparts at a median follow up of 16 months. A reduction in the composite kidney outcome (defined as sustained profound decline in eGFR, chronic dialysis, or transplant) was also observed among patients randomized to receive empagliflozin irrespective of baseline renal function (HR for patients with vs. without CKD: 0.53 vs. 0.46, respectively, p=0.78) (77). Whether the cardiorenal benefits of SGLT2i seen in the general population can be extrapolated to the transplant population awaits further studies. Limited prospective and retrospective studies in the setting of solid organ transplantation showed that SGLT2i has a modest effect on glycemic control and a favorable effect on weight reduction (78-80). In a single-center, prospective, double-blind study consisting of 44 kidney transplant recipients with PTDM randomized to receive either empagliflozin (n=22) or placebo (n=22) for 24 weeks, a significant reduction in A1C was observed among empagliflozin-treated patients compared with their placebo-treated counterparts (-0.2% vs. 0.1%, p=0.025). A significant reduction in body weight was also observed (-2.5 kg vs. +1.0 kg, respectively p=0.014). There were no significant differences in adverse events, immunosuppressive drug levels, or eGFR between the two treatment groups (78). A small retrospective single-center observational study consisting of 97 heart transplant recipients with PTDM demonstrated that empagliflozin-based treatment (n=20) resulted in a significant reduction in body weight (p=0.05), BMI (p=0.04), mean furosemide dose (p=0.05), and systolic and diastolic blood pressure (p=0.03) compared with control (non-empaglifloxin-based treatment, n=77) at 12-month follow-up. There was a statistically non-significant mean reduction in A1C of 0.6%. No serious adverse events were observed (80). Based on the study findings the investigators suggest that SGLT-2 inhibitors are suitable for use following heart transplantation (81). Reported adverse effects associated with SGLT2 use include increased risk for urinary tract infections, genital candidiasis, euglycemic diabetic ketoacidosis, and acute kidney injury. The latter presumably due to its effects on afferent arteriolar vasoconstriction and its natriuretic and diuretic effects. Distal limb amputation and Fournier gangrene associated with SGLT2i use have not consistently been demonstrated.

There have been no consensus treatment guidelines for PTDM. The choice of individual agents should be based on potential advantages and disadvantages of different classes of agents. Unless contraindicated, GLP1 receptor agonist may be considered in kidney transplant recipients with established CVD (or multiple CVD risk factors) whereas SGLT2i may be the preferred agent for those with a history of heart failure. SGLT2i use may have the added benefit of renoprotection independent of its glucose-lowering effects. Failure to achieve glycemic control despite multiple antihyperglycemic agent combination therapy generally requires initiation of insulin therapy. The 2014 international consensus guidelines on the screening, diagnosis, and management of early posttransplant

hyperglycemia and PTDM is shown in Figure 3. Although evidenced-based recommendations are lacking, within the past several years newer injectable antidiabetic agents have increasingly been used. The authors' suggested protocol for screening, diagnosis, and management of early post transplantation hyperglycemia and PTDM is shown in Figure 5 (practice varies among centers).

PTDM screening and management	Comments
PTDM Screening Baseline A1C at 3 mo after transplant, then at 6 mo,12 mo, then annually Treat vitamin D deficiency if applicable	If screening A1C is in the prediabetic range, patients should be counseled on dietary and lifestyle modification and A1C monitored every 3 months.
Newly diagnosed PTDM Dietitian and/or diabetic educator referral recommended	
Dietary modification Dietary modification with carbohydrate controlled diet For diabetic dyslipidemia: Diet low in saturated fats and cholesterol and high in complex carbohydrates and fibers **AHA guidelines (in non-transplant settings)** Limit cholesterol intake to < 200 mg/day for individuals with diabetes mellitus < 7% of calories from saturated fats; 2% to 3% of calories from trans-fatty acids ≤ 2400 mg of sodium per day > 25 g of dietary fiber per day and 2 servings of fish per week	Dietary guidelines for vegetarians are lacking. Flax seeds (or flaxseed oil) and chia seeds are alternative sources of omega-3 fatty acid.
Lifestyle modification Exercise, weight reduction or avoidance of excessive weight gain, smoking cessation	Define realistic goals (e.g. target weight loss of 5% to 10% of total body weight)
Pharmacologic therapy **2009 KDIGO guidelines:** Target A1C 7.0% to 7.5%, not to fall below 6% (particularly if hypoglycemic reactions are common) **Treatment options:** oral agents, GLP-1 agonist, DDP-4 inhibitors, SGLT2 inhibitors, insulin (see text and figure 4) Consider diabetologist referral if A1C remains at 9.0% or higher.	Acute, marked hyperglycemia generally requires inpatient management. Consider insulin drip when glucose ≥ 400 mg/d.
Adjustment or modification of immunosuppression (SEE COMMENTS) Safe rapid prednisone taper to 5 mg daily maintenance dose Routine corticosteroid withdrawal is NOT recommended Consider cyclosporine-based immunosuppression if multiple PTDM risk factors are present Tacrolimus to cyclosporine switch may be considered in low immunological risk patients (variable results)	Clinicians must be familiar with the patient's immune history before manipulating immunosuppressive therapy. Immunosuppression adjustment to reduce PTDM risk in high immunological risk patients is not recommended
Monitoring PTDM A1C every 3 months. Screening for microalbuminuria, regular ophthalmologic examination, aggressive treatment of hyperlipidemia and hypertension, regular foot care	

Figure 5. Suggested screening and management of PTDM (opinion-based)
mo, month; AHA, American Heart Association; KDIGO, Kidney Disease Improving Global Outcomes

SUMMARY

PTDM is a common complication after solid organ transplantation and has variably been reported to be associated with increased morbidity and mortality. Risk stratification, intervention to minimize risk and early diagnosis may alleviate the incidence of PTDM and improve outcomes following solid organ transplantation. The 2014 International Consensus Guidelines suggest expanding screening tests for PTDM using postprandial glucose monitoring and HbA1C test. However, the latter should be used with caution in the early posttransplant period. A normal A1C does not exclude the diagnosis of PTDM in the presence of early posttransplant anemia and/or dynamic kidney allograft function. Whether intravenous iron therapy and/or the use of erythropoietin stimulating agent result in falsely low A1C levels remains to be studied. Currently early initiation of basal insulin therapy in patients with new onset hyperglycemia during the first post transplantation week to preserve β-cell function and progression to overt PTDM cannot be routinely recommended. Management of established late PTDM should follow the conventional approach and guidelines established for the general population. When lifestyle modification fails to achieve glycemic control, medical intervention is often necessary. The choice of one antihyperglycemic agent over the other should be based on the potential advantages and disadvantages of individual agents. Metformin appears safe in kidney transplant recipients with mild to moderate renal impairment (eGFR 30-60 mL/min). SGLT2 inhibitor has been suggested to be suitable for use following heart transplantation. Its use after kidney transplantation should be individualized. Similar to the general population, insulin therapy should be considered in individuals with suboptimal glycemic control despite multiple antihyperglycemic agent combination therapy.

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