Post-Transplant Diabetes: Prevalence, Risk, and Management Challenges

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Abstract
The prevalence of diabetes and diabetic nephropathy is increasing, especially in middle eastern countries. Many patients reach end-stage renal disease and either start dialysis or consider preemptive transplantation. Even a higher number of patients develop post-transplant diabetes, which imposes an even higher risk on graft survival and outcomes post-transplantation. Recently, in the UAE, a renal transplant service has been initiated. Because the population is considered at high risk for post-transplant diabetes, we wrote this review article to discuss the prevalence, risk factors, diagnostic criteria, and management, including lifestyle interventions, manipulation of immunosuppressant agents, and suggested algorithms for the use of oral hypoglycemic agents used in the management of post-transplantation diabetes mellitus. We also discussed the specific indications for each of the oral hypoglycemic agents.

Introduction
Data from the USA suggests that chronic kidney disease is one of the major causes of morbidity as well as mortality, with almost 26 million patients suffering from end-stage renal disease (ESRD). More than 468,000 individuals in the USA are on regular dialysis [1]. Diabetes is by far the commonest cause of kidney disease and accounts for 44–50% of all causes of ESRD [2].

The advent of the calcineurin inhibitor (cyclosporine) has paved the way for a new era in transplant outcomes. Further, the new improvements in immunosuppressive regimens have resulted in significant improvements in patients and graft survival. Kidney transplant is considered more cost-effective than dialysis resulting in better outcomes and improves the quality of life [3, 4]. The use of the new regimens was hoped to reduce complications of steroids, namely diabetes, and hyperglycemia, but, in fact, even without steroids, the risk remained high [5].

Limited data is available from the region on the prevalence and risk factors for post-transplant diabetes. In a study from Morocco, Zbiti et al. [6] found a prevalence of post-transplant diabetes of 15% and that old age use of cyclosporine and steroids are the main risk factors. Two
studies from Iran discussed the risk factors for post-transplant diabetes. They reported a family history of diabetes, hypertension, polycystic kidney disease, high triglyceride level, and dose of cyclosporine and steroids predicted post-transplant diabetes [7, 8]. In this review article, we discussed the latest recommendations for diagnosis and prevalence of PTDM, epidemiology, risk factors, and how to modify these factors, perioperative evaluation, and management, and finally, how to manage individuals with post-transplant diabetes.

**Literature Search**

We conducted a search in PubMed with the search terms post-transplantation, diabetes mellitus, and management. The initial search included clinical trials, meta-analysis, randomized controlled trials, review articles, and systematic reviews. The initial search retrieved 159 articles; when used the filter of 10 years, the number of articles retrieved was 116. We limited our search to full texts only and the final number of articles was 114 articles.

### Diagnosis of PTDM

In the first international consensus guidelines for NO-DAT, the committee agreed to adopt the WHO criteria for the diagnosis of diabetes shown in Table 1 [9–11]. In the following meeting in 2013, the consensus changed the name to post-transplant diabetes mellitus (PTDM) as many cases of diabetes diagnosed after transplant were preexisting. The consensus also re-evaluated the timing for diagnosis of PTDM to exclude the immediate postoperative period, as many individuals would receive high doses of steroids, and the resultant hyperglycemia might not persist after hospital discharge [12, 13].

| Criteria                          | Level, mg/dL | Level, mmol/L | Comment                  |
|----------------------------------|--------------|---------------|--------------------------|
| Fasting glucose                  | 126          | 7             | On more than one occasion|
| Random glucose                   | 200          | 11.1          | With associated symptoms |
| Two-hour glucose after a 75-g OGTT| 200          | 11.1          |                          |
| HbA1c**                          | 6.5%         |               |                          |

* PTDM should be considered after an individual being discharged from the hospital. ** HbA1c should not be used alone for screening for PTDM, in the first year.

The use of HbA1c as a screening method for PTDM has been criticized as it has less reliability in detecting glucose intolerance within the first year after transplant due to reduced red cell survival [14, 15]. It has been recommended that HbA1c be used along with other criteria for diagnosing PTDM in the first 12 months. Following the first year, it is considered more reliable provided the general conditions that affect HbA1c are evaluated.

The question that arises is how long after transplant we would consider diabetes PTDM rather than type 2 diabetes. Currently, the term PTDM applies to any form of diabetes that develops after transplant regardless of when it developed; this might be one or even 20 years after transplant [5]. As hyperglycemia and glucose intolerance tend to become more prevalent with age, the significance of considering a diagnosis of PTDM within first year or first five years needs to be decided [5].

In summary, post-transplant diabetes is considered a diagnosis in all patients who present with hyperglycemia and fulfil the criteria for diagnosis of diabetes after transplant. It is essential to remember the exclusion of those who develop hyperglycemia within the first few weeks post-transplant due to the impact of high-dose steroids given during this period. Some authors suggest an upper limit period of 5 years post-transplant given the impact of age on the incidence of diabetes.

### Risk Factors and Pathophysiology of PTDM

Traditional risk factors for diabetes increase the likelihood of PTDM. In addition, there are transplant-related factors that further increase the risk. In many patients, these risk factors overlap, increasing the risk further [16]. The traditional risk factors might be present before transplant, and some of them might develop after transplant, like obesity and a sedentary lifestyle.
Our understanding is that the pathophysiology of PTDM is slightly different from T2DM; though it is multifactorial, like for T2DM, some mechanisms are common as well, like insulin resistance, which is a significant pathophysiologic mechanism for PTDM [17]. However, there is recent evidence suggesting impaired insulin secretion may also be important [17]. Various pathogenic mechanisms associated with different risk factors for PTDM are shown in Table 2. Hence, it is of prime importance to understand the risk factors and pathophysiology of PTDM as clinicians (nephrologists, endocrinologists, and transplant physicians) involved in the care of kidney transplant patients so we can implement strategies that decrease or modify the risk and incidence of development of PTDM and improve graft survival.

In this review, we will discuss the different risk factors and pathophysiologic mechanisms known to cause PTDM. We will consider the risk factors for developing PTDM, pre-transplant, post-transplant, and factors associated with the allograft (Fig. 1).

### Non-Modifiable Risk Factors

**Pre-Transplant**

These are mostly the traditional risk factors, which include ethnicity, advanced age, genetic predisposition, family history of diabetes type 2, male gender, prior use of steroids for glomerular renal disease or other systemic diseases, like systemic lupus nephritis, and impaired glucose tolerance (IGT) or gestational DM [18, 19].

**Ethnicity**

Certain ethnic groups are known to have a higher incidence of diabetes, including African Americans, South Asians, and Hispanics [20, 21]. Blacks are twice as likely to develop PTDM than whites [13]. The increased risk for PTDM in blacks is related to differences in the pharmacokinetics of immunosuppressives [22].

**Age**

Age is the most potent risk factor for PTDM [21]. Multiple studies revealed that increasing age is associated with a higher risk of PTDM. In fact, for every 10-year increase in age, the likelihood of PTDM increases by almost 50%. Many studies suggested age >45 years is associated with a higher risk for PTDM [23, 24]. The risk of PTDM increases with age by about 2.9-fold, while age above 60 years is associated with a 2.6-fold increased risk [25, 26].

**Genetic Predisposition:**

Human leukocyte antigens (HLA), such as HLA A28, A30, B27, and B42, are associated with an increased risk of PTDM [16, 18]. The risk also increases with polymorphisms in certain genes like HNF-4A, insulin receptor substrate 1 gene, and *TCF7L2* gene.

**Polycystic Kidney Disease**

ADPKD confers an increased risk of PTDM. ADPKD is caused by the mutation in one of two genes: PKD1 or PKD2 in most cases. The mutations of PKD1 or PKD2 might cause a genetic predisposition to metabolic abnormalities [27]. A most recent study from the UK shows PTDM risk

| Mechanism                                      | Risk factors                                                                 |
|------------------------------------------------|------------------------------------------------------------------------------|
| Impaired insulin release                       | Steroid                                                                      |
|                                               | CNIs (tacrolimus, cyclosporine)                                              |
|                                               | CMV infection                                                                |
| Increased peripheral insulin resistance        | Steroids, obesity, HCV infection                                             |
| Increased gluconeogenesis                      | CNIs (tacrolimus, cyclosporine) → hypomagnesemia → insulin resistance        |
| Reduced glycoegenesis                         | Steroids                                                                     |
| Impaired pancreatic beta-cell function         | Steroids                                                                     |
| Reduced glucose uptake                         | CNIs (tacrolimus, cyclosporine)                                              |
| Direct pancreatic beta-cell toxicity           | CNIs (tacrolimus, cyclosporine)                                              |
| Reduced insulin gene expression                | CNIs (tacrolimus, cyclosporine)                                              |
| Hypomagnesemia                                 | Sirolimus                                                                    |
| Decreased pancreatic cell proliferation       | Genetics, ADPKD, race, male donor, deceased donor                             |
was not significantly higher in ADPKD patients than in non-ADPKD transplant patients, but this is a single-center study [27]. However, there is inconsistency in published reports on whether ADPKD is associated with an increased risk for PTDM. In one meta-analysis, the relative risk for the development of PTDM was 1.92 (95% confidence interval: 1.36–2.70) [28]. The International PTDM Consensus guidelines recommend identifying kidney transplant candidates at increased risk for PTDM and advocate preventive measures to attenuate risk for PTDM [29].

Other Pre-Transplant Risk Factors
A history of gestational diabetes or preexisting glucose intolerance may increase the risk of PTDM. Steroid-induced glucose intolerance, whether related to the treatment of primary renal disease or an unrelated systemic disorder, also increases the risk of PTDM. The risk of diabetes persists regardless of cessation of steroids before transplant [16, 18, 21].

Transplantation-Associated Risk Factors
Donor factors including graft type, age, and gender are considered non-modifiable. Recipients of deceased donor grafts are at a higher risk of PTDM. This has been explained by the higher proinflammatory cytokine response induced by the deceased graft compared to the living donor allograft. The relative risk value has been estimated to be close to 4 [16, 18, 30].

Modifiable Risk Factors (Pre-Transplant and Post-Transplant)

Obesity, Metabolic Syndrome, and Sedentary Life
All these factors can be present before or after transplant and are potentially modifiable. Obesity has been found to be associated with an increased risk for PTDM in most studies. As per USRDS data, the relative risk of PTDM is as high as 1.73, \( p < 0.0001 \) if the BMI is >30 [21]. There is a linear increase in risk for PTDM with every 1 kg above 45 kg [21]. Obesity, body fat percentage, and body fat pattern play a role in inducing insulin resistance [31, 32]. In a non-transplant setting, studies on healthy women reveal that the metabolic syndrome phenotype is associated with insulin resistance and IGT more than lower body or female-type obesity; however, limited data is available in transplant patients [33]. In the Patient Outcomes in Renal Transplantation study, metabolic syndrome has been described to be an independent risk for PTDM (HR = 3.46, 95% CI: 2.40–4.98, \( p < 0.0001 \)) [32].

Hepatitis C Infection
Hepatitis C virus (HCV) infection has been linked to an increased risk of DM in the general population [34]. Moreover, evidence suggests that HCV infection increases the risk for PTMD [35]. There is a 25.6% risk to develop PTDM if the patient is HCV positive compared to 14.4% in HCV negative patients [27]. Other study found an ad-
justed odd ratio for PTDM approaching 4 if patients are HCV positive, this risk may potentially increase with the use of tacrolimus [35, 36]. Pathogenetically, hepatitis C is associated with reduced insulin sensitivity; however, it has not been shown to affect insulin secretion or hepatic insulin uptake [37]. A small study revealed that prior treatment of HCV infection reduces the risk of PTDM [38].

Post-Transplant Modifiable Risk Factors
Immunosuppressive drugs, CMV infection, and acute rejection episodes and their treatment are the most important modifiable risk factors. Immunosuppressive drugs are the most important risk factor for the development of PTDM. Individualization of immunosuppressive drugs can be considered to reduce the risk of PTDM, but such manipulation should not jeopardize graft survival.

Corticosteroids
Corticosteroids is one of the mainstay immunosuppressive drugs for post-transplant immunosuppression protocol. It has three important roles in kidney transplants.
1. High dose steroid as part of induction protocol used perioperatively.
2. Lower tapering dose as maintenance therapy.
3. High-dose steroids for the treatment of acute rejection episodes.

Pathogenic Mechanisms
Corticosteroids predispose to the development of diabetes and post-transplant diabetes mellitus. Corticosteroids cause hyperglycemia through several mechanisms: induction or worsening of preexisting insulin resistance, inducing both gluconeogenesis as well as glycolysis, and increasing both fasting and postprandial hyperglycemia while decreasing insulin secretion. In the long-term, steroids stimulate appetite and induce weight gain. The higher the dose of steroids, the higher the risk of PTDM; hence, induction protocols are more diabetogenic than maintenance doses [16, 39]. In one study, an increase in the dose of prednisolone by 0.01 mg/kg/day above 5 mg is associated with a 5% risk of developing PTDM [40, 41]. On the other hand, complete cessation of steroids does not completely negate the risk of PTDM [42].

The role of steroid-free regimens has been evaluated in a retrospective study and has been found to eliminate the risk of PTDM in African Americans and Caucasians but not in Hispanics recipients [43]. In a retrospective analysis of a large transplant database, Luan et al. [44] concluded that steroid-free immunosuppression significantly reduced the likelihood of PTDM compared with those containing steroids. They reported a cumulative incidence of 12.3% in steroids free regimen, while the incidence increased to 17.7% with steroid use (p = 0.001).

Early steroid withdrawal versus low maintenance dose steroid has been evaluated in a prospective trial for 6 months to 5 years post-kidney transplant; the study has not shown any significant impact on the incidence of PTDM among both groups, which suggests that at the low dose, the effects of corticosteroids like decreased insulin sensitivity and gluco-regulation do not occur [42].

Calcineurin Inhibitors (Tacrolimus, Cyclosporine)
CNI-based immunosuppression is the cornerstone of immunosuppressive regimes for a kidney transplant. Currently, tacrolimus is the most commonly used CNI, and it constitutes 93% of immunosuppressive regimes as per the Organ Procurement Transplant Network/Scientific Registry of Transplant Recipient (OPTN/SRTR) Annual Report 2018 [45]. The diabetogenic impact of CNIs is more for tacrolimus compared to other CNIs [43]. Although debatable, the diabetogenic effect is likely to be dose-dependent [46]. Despite the increased risk of PTDM associated with tacrolimus, CNI is preferred due to its demonstrated superior efficacy and safety [46, 47].

Pathogenic Mechanisms
There are multiple mechanisms known through which CNI are thought to cause PTDM (Table 1).
1. Impaired insulin secretion.
2. CNIs increase islet cell apoptosis and reduces beta cell mass.
3. Calcineurin plays a role in the survival of pancreatic beta cells at the molecular level. Hence, CNI decreases the survival of beta cells. In INS-1E β-cells, cyclosporine and tacrolimus inhibit both basal and glucose-stimulated insulin secretion after prolonged exposure. They alter mitochondrial function and number by interacting with transcription factors that modulate β-cell growth [1]. Besides, CNI leads to reduced insulin gene expression [48].
4. Decreased peripheral Insulin resistance. In vitro studies suggest that CNI reduce the number of type 4 glucose transporters (GLUT-4) in the cell membrane of the adipose tissue; hence it leads to inhibited uptake of glucose molecules by the cells. GLUT-4 is insulin-regulated and is present mainly in striated muscle and adipose tissue, allowing the movement of glucose inside the cell cytoplasm. By inhibiting GLUT-4, CNIs lead to hyperglycemia [48].
5. Hypomagnesemia: tacrolimus is known to cause hypomagnesemia, which is an independent risk factor for insulin resistance and hyperglycemia [16].

Mammalian Target of Rapamycin Inhibitors (Everolimus and Sirolimus)

Sirolimus and everolimus have been used in several immunosuppressive protocols both with CNI and without CNIs. They were used for CNI avoidance or CNI conversion protocols.

Earlier data suggested that the risk of PTDM with sirolimus were related to the combination with tacrolimus; however, current knowledge suggests that it is an independent risk factor for PTDM [49, 50]. As the risk of diabetes is lower with sirolimus, case reports suggest that substituting CNIs with sirolimus improves glycemic control in PTDM [51].

Pathogenesis

Impaired insulin secretion, reduced insulin signal transduction, and decreased pancreatic cell proliferation are the possible pathogenic mechanisms resulting in PTDM associated with sirolimus.

CMV Infection

CMV is one of the common opportunistic infections post-kidney transplants. CMV infection is associated with an increased risk for the development of PTDM. CMV is considered to carry an independent risk factor for PTDM. The relative risk for PTDM is 1.94 if patients are CMV positive compared to negative individuals [52]. CMV induces proinflammatory cytokines and causes destruction of the pancreatic beta cell; however, further studies are required to establish these mechanisms further [16].

Management of PTDM

Pre-Transplant Detection of High-Risk Population

Pre-transplant assessment is essential for the detection, prevention, and treatment of high-risk populations. Patients should be screened to tailor and manipulate immunosuppressive treatment to reduce the risk of PTDM. Many factors increase the risk for PTDM, including age >45 years, people with a previous history of PTDM, gestational diabetes, HCV infection, IGT, features of metabolic syndrome, and BMI more than 30 kg/m².

Bergrem et al. [53] evaluated 889 patients with their first single kidney transplant without previous diabetes. They reported the low sensitivity of fasting blood glucose (FBG) in detecting PTDM. Furthermore, performing OGTT in patients with an FBG of 92–125 mg/dL allowed detection of more than 80% of pre-transplant diabetes [16]. Thus, for screening, it is recommended to use FBG and OGTT. HbA1c is not recommended for screening given the limitations in patients with ESRD [53, 54].

Pre- and Perioperative Management of Hyperglycemia and Diabetes

The stress related to surgery and the use of high doses of steroids during the induction period frequently induce hyperglycemia in the early post-transplant period. Insulin infusion is used perioperatively, as appropriate, to control hyperglycemia [55, 56]. In one retrospective study, the development of perioperative hyperglycemia after transplantation significantly predicted a 4-fold increase in the risk of PTDM at 1-year post-transplant [57].

There is no internationally agreed approach for screening or managing PTDM at the pre-, peri-, or post-transplant period. The approach uses the general management of diabetes in the general population. For surgical patients, the glycemic goals recommended for noncritically ill patients treated with insulin is a FBG value <140 mg/dL (<7.8 mmol/L) and a random glucose value of <180 mg/dL (<10.0 mmol/L). Once patients begin to eat after surgery, the regimen can be changed to subcutaneous insulin (basal or basal-bolus, as appropriate) if hyperglycemia persists. Many patients can be weaned off insulin before discharge with a decline in postoperative stress and a reduction of steroid doses. Patients discharged home on insulin therapy will need follow-up by a diabetologist for optimal glycemic control [55].

Post-Transplant Screening for PTDM

Patients with prediabetes: Transplant recipients with impaired fasting glucose (IFG) or IGT are considered to have a post-transplant prediabetes state. In such cases, the main aim of management is to avoid further progression to diabetes. Lifestyle modification focusing on dietary adjustment, weight reduction, and physical exercises is warranted, though data on the benefits of lifestyle modification in this group are limited and are concluded from studies in non-transplant patients at risk for type-2 diabetes mellitus [58, 59]. Those patients should continue to have routine monitoring for PTDM. Additionally, a patient diagnosed previously with diabetes but whose symptoms have resolved should be closely monitored as those individuals are at higher risk for the development of diabetes [13].
Post-Transplant Screening and Monitoring

Patients at risk for PTDM and discharged without hyperglycemia are recommended to be screened for PTDM with fasting plasma glucose testing as follows [9, 32, 58]:

- weekly for 1-month post-transplant,
- four times in the first year (every 3 months),
- then, annually.

If IFG is detected at any time, particularly at the 3rd and 6th months (the risk of PTDM is highest during the first 6 months after transplantation), an OGTT should be performed to confirm the diagnosis. Patients with IFG or IGT should receive lifestyle counseling, including expert dietary advice and active physical activities, as tolerated. Among kidney transplant recipients in whom PTDM was confirmed with either a diagnostic fasting blood sugar (>126 mg/dL [7 mmol/L]) or with a positive glucose tolerance test (>200 mg/dL [11.1 mmol/L], 2 g post 75 g glucose), persistently for more than 3 months post-transplant, they should be referred to a diabetic clinic for further evaluation. After hospital discharge, HbA1c is reliable for monitoring glycemic control [57–59].

Transplant Recipients with Confirmed PTDM

PTDM can manifest as mild hyperglycemia responding to dietary treatment alone or as severe hyperglycemia necessitating insulin treatment. Once a diagnosis of PTDM has been established based on the above monitoring measurements, patients should be monitored with HbA1C assay measured routinely every three months and with FBG at each visit [9, 58]. The optimal glycemic targets for kidney transplant recipients with PTDM are similar to the general population with diabetes and should consider factors such as duration of diabetes, comorbid conditions, risk of hypoglycemia, and life expectancy.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend an HbA1c goal of 7–7.5% for kidney transplant recipients [60]. However, a higher HbA1c (e.g., <8%) should be considered for elderly recipients and those with a limited life expectancy. On the other hand, the American Diabetes Association (ADA) set a general HbA1c target of <7% and recommended a three-month interval monitoring [58].

Manipulation of Immunosuppression

The immunosuppressive regimen may be started before the recipient proceeded to a kidney transplant operation to reduce the recipient’s immune function. The selection of regimen is tailored according to the recipient’s circumstances and, in particular, the perception of immunological risk [9, 55, 61]. Presently, there is no consensus regarding the choice of an immunosuppression regimen to prevent PTDM [55, 62, 63]. In the modern era of immunosuppression, the regime should be tailored as per immunologic risk versus the risk of developing complications like PTDM in a kidney transplant recipient.

Immunosuppressive drugs are among the most important risk factors for the development of PTDM. Individualization of immunosuppressive drugs can be considered to reduce the risk of PTDM, but such manipulation should not jeopardize graft survival.

Reduction in the dose of corticosteroid during the first year after transplantation has considerably improved glucose tolerance, so steroid dose should be tapered quickly in low immunologic risk patients with a high risk of PTDM and steroid-sparing protocols should be tailored to each patient. A large retrospective trial for renal transplant recipients reported significant benefits concerning PTDM at 3 years for the corticosteroid sparing regimen at initial hospital discharge compared to the patient on a corticosteroid-containing regime [18]. On the other hand, other randomized controlled studies comparing corticosteroid withdrawal on post-transplant day versus no withdrawal showed better glycemic control, although few patients showed PTDM requiring insulin at 5-years post-transplant in the corticosteroid avoidance group [13, 18]. However, any steroid dose reduction or steroid avoidance should be balanced against the risk of acute rejection, as any steroid reduction or steroid avoidance poses the risk of rejection, hence requiring pulse/high-dose steroid, which ultimately increases the risk of PTDM [18, 61]. Mycophenolate should be carefully monitored to prevent graft rejection, particularly in a patient on corticosteroid tapering dose of corticosteroid withdrawal [9, 48, 61].

For patients with a high risk of PTDM and low immunological risk, the ideal choice of immunosuppressive regimen is belatacept based or cyclosporine [9], while if the patient with high immunological risk developed PTDM and their insulin and blood sugar are uncontrolled, they should consider switching tacrolimus to cyclosporine [9]. The use of alemtuzumab (an anti-lymphocyte induction agent) and belatacept (a recently introduced selective co-stimulation blocker) as induction therapies in kidney transplantation has been associated with a reduced incidence of PTDM [9, 63]. Studies have shown that the effect of tacrolimus on insulin release is dose-related, and reducing the tacrolimus dose by 30% within the target level can improve insulin release by 24% [18, 61].
Furthermore, studies investigating the conversion of tacrolimus to cyclosporine for better glycemic control have reported variable results, even in studies comparing cyclosporine to tacrolimus showed that there is no much difference in long-term glucose metabolism and no benefit in switching patients on tacrolimus to cyclosporine who experience high glucose levels for >3 months’ post-transplantation [61]. In high-risk patients, tacrolimus-based immunosuppression with steroid minimization provides the best balance between PTDM and acute rejection incidence [64]. Finally, it is recommended that the immunosuppressive regimen be decided based solely on the best outcome for overall patient and graft survival, regardless of PTDM risk [65].

In summary, the management of renal transplant patients should include pre-transplant baseline assessment and careful selection of appropriate immunosuppressive therapy for each patient individually, especially those at high risk for developing PTDM after transplantation. In addition, patients should be monitored often after transplantation, especially patients with abnormal glucose metabolism [58, 66]. The evaluation and management of patients with PTDM should be in close cooperation between the transplant team and endocrinologists [48, 55].

**Role of Lifestyle Modification in Prevention and Treatment of PTDM**

Many clinical trials have confirmed the beneficial role of lifestyle intervention in delaying or preventing type 2 diabetes [67–69]. Data from the USA have suggested a significant increase in the prevalence of obesity at the time of transplant, and since pre-transplant obesity correlates with increased insulin resistance, lifestyle modification would seem a reasonable intervention [70]. However, the timing of the intervention is uncertain. Leavey et al. [71], in the DOPPS study, reported that higher BMI correlated with reduced mortality in patients on hemodialysis [61]. Recent reports suggested that higher BMI with higher muscle mass is more protective than high-fat mass [72]. This suggests that an intervention aimed at increasing lean body mass before a transplant would reduce the risk of PTDM and improve graft and patient survival [73–75].

On the other hand, patients on hemodialysis self-report reduced physical activity; this is more so during dialysis than non-dialysis days. Many factors contribute to reduced physical activity, mainly the time spent during dialysis treatment, anemia, hypervolemia, and uremic cachexia. These factors contribute to the difficulty of starting an effective lifestyle adjustment in the pre-transplant period [76, 77].

**Management of PTDM**

Treatment of post-transplant diabetes aims at reducing long term micro and macrovascular complications, reduce osmotic symptoms and prevent rejection [7]. Treatment of PTDM can be divided into different stages. The first stage is the immediate postoperative period, in which hyperglycemia may be related to the use of different immunosuppressive treatments. The second period is the outpatient management of PTDM.

**Management of Glucose Excursions during the Immediate Post-Transplant Period**

During the initial phase, many factors might contribute to fluctuations in blood glucose, including the use of high steroid doses, weaning of steroids after the first week, stress, pain, increased nutritional intake, parenteral nutrition, and rapid improvement in renal function after transplant. Patients with post-transplant hyperglycemia require frequent monitoring of blood glucose [78]. Given the high insulin requirement during this period, insulin therapy is frequently used. The use of insulin infusion allows titration of insulin doses to prevent significant excursions in blood glucose. Many studies in the post-transplant setting have proved the efficacy and safety of intravenous insulin regimens [79, 80].

It is essential to mention here that specific glycemic targets for the immediate post-transplant period have not been established. However, a study by Hermayer et al. [81] randomly treated two groups of post-renal transplant recipients using intensive intravenous insulin to two different targets: blood glucose (BG) = 70–110 mg/dL; or a control group treated with subcutaneous insulin (BG = 70–180 mg/dL). These authors concluded that the primary outcome of delayed graft function was not different between the two groups. However, the intensively treated group was at higher risk for rejection episodes [81]. Hence, the practice guidelines for inpatient management suggest 140–180 in intensive care and premeal of <140 mg/dL and postmeal of <180 mg/dL in a nonintensive care setting [82]. Patients who continue to have hyperglycemia and osmotic symptoms after discharge from hospital might need to continue with insulin therapy in the long term.

**Management of PTDM in Outpatient Setting**

There are no specific recommendations for the best single or combination therapy for patients with PTDM. An overview of evidence for oral agents is provided here,
followed by the suggested algorithm. It is essential to mention that the suggested algorithm is extrapolated from studies in non-transplant patients with type 2 diabetes.

**Biguanides**

Metformin is effective in stable kidney transplant recipients. Kurian et al. [83] retrospectively evaluated the safety and efficacy of metformin compared to thiazolidinediones. These authors included both patients with pre-existing diabetes as well as post-transplant diabetes. They concluded that both classes are safe and effective in post-renal transplant recipients [83]. Safety and efficacy of metformin have been reported in many other publications [84].

Metformin should be used cautiously or discontinued during acute hospitalization, congestive heart failure, and significant active infection. It is recommended to hold or discontinue metformin in a planned intravenous contrast study or drop in the GFR below 30 mL/min.

**Sulphonylureas**

Data on the efficacy of sulphonylureas in transplant patients is limited. Sulphonylureas did not change the cyclosporine pharmacokinetics in patients with PTDM [85]. Sulphonylureas are associated with an increased risk of hypoglycemia [86], in a study by Tuerk et al. [87]. Gliquidone has proved as effective and safe as rosiglitazone PTDM.

**Glitazones**

Few studies have proven the effectiveness of TZDs in the management of PTDM [83, 88–91]. When compared to metformin in renal transplant patients with PTDM, TZDs have proven effective and safe [83]. Luther and Baldwin [90] also assessed the safety of pioglitazone as an add-on therapy to insulin or sulphonylureas; they concluded that pioglitazone is safe and effective as an add-on therapy in PTDM. Another study showed that the use of rosiglitazone was effective and was not associated with any changes in serum creatinine or cyclosporine and tacrolimus blood levels [91]. A similar study compared pioglitazone and insulin in PTDM; the authors concluded that both agents reduce HbA1c, result in a better lipid profile, and have similar weight gain. None of the two agents showed any interactions with immunosuppressive medications [92]. Many other studies concurred with these findings; Luther and Baldwin [90] found similar findings in a single-arm study using pioglitazone in PTDM. Similarly, Werzowa et al. [89] reported similar effects in a three-arm study comparing pioglitazone, vildagliptin, and placebo in PTDM.

TZDs are associated with an increased risk of weight gain, heart failure, and reduced bone mass and an increased risk of fractures. The impact of TZDs on the risk for heart failure after transplant is not well known.

**DPP-4 Inhibitors**

In a Cochrane meta-analysis, treatment with a DPP4 inhibitor had uncertain effects in patients with post-transplant diabetes [93]. However, small retrospective trials have shown DPP4 inhibitors to be effective and safe in PTDM [89]. Vildagliptin appeared to offer an effective alternative in reducing HbA1c with a low risk of hypoglycemia in PTDM. Furthermore, no reports of the interaction of DPP4 inhibitors with any of the immunosuppressive medications [94]. The role of DPP4 inhibitors in preventing PTDM is being evaluated in a randomized controlled double-blinded study using vildagliptin (PRODIG study) [95]. In a study by Bae et al. [96] who evaluated the use of DPP4 inhibitors in post-transplant diabetes, they reported a beneficial effect of Linagliptin which demonstrated superior glucose-lowering efficacy and minimal effect on cyclosporine trough levels in comparison with other DPP-4 inhibitors in kidney transplant patients with diabetes.

**GLP-1 Agonists**

The initial concerns were reduced gastric emptying and reduced bowel motion that might interfere with immune-suppressive drug absorption. In a small study, liraglutide did not alter the concentration of tacrolimus in patients with PTDM [97]. Data on the other GLP1 analogs in post-transplant diabetes is limited.

**SGLT2 Inhibitors**

Similar to other medications, little evidence is available for SGLT2 inhibitors in PTDM. Evidence for SGLT2 inhibitors in patients with diabetes with or without chronic kidney disease suggests that they reduce HbA1c, FBG, systolic and diastolic blood pressure, and hyperkalemia [98–100]. Data from renal outcome trials suggests that SGLT2 inhibitors have a renoprotective effect in reducing renal death, doubling of serum creatinine delay time to dialysis. These findings were seen in patients with an eGFR of 30–60 mL/min/m² [101–103].

The increased risk of genitourinary infections associated with SGLT-2 inhibitors in those with a previous history is a concern, especially in immunocompromised transplant patients. There is also an increased risk of vol-
Preoperatively had risk factors for PTDM

Therapeutic lifestyle intervention and consider manipulation of immunosuppressive medications

Postoperative screening
PTDM diagnosed based on diagnostic criteria (table 1)

Yes

Therapeutic lifestyle intervention and consider manipulation of immunosuppressive medications

Use insulin IV or SC in the immediate postoperative period

Target blood glucose 140-180 mg/dl

No

Therapeutic lifestyle intervention and consider the manipulation of immunosuppressive medications

Use oral agents or/and insulin to achieve targets after discharge

Target HbA1c should be individualized but a general target is <7%. UAE SMBG to ensure achieving targets*

* KDIGO suggests <7.5%, a higher target <8% is acceptable for selected patients

Fig. 2. Glycemic targets in the early and late post-transplant periods.

Metformin + lifestyle intervention

The dose should be adjusted based on eGFR and discontinued at eGFR<30ml/min/m2
Should be used cautiously during hospitalization and discontinued before contrast studies

1st Line

SGLT2 inhibitors

2nd Line

GLP1 agonists

DPP4 inhibitors

Sulphonylureas

Pioglitazone

Patient selection

Proteinuria
eGFR>30ml/min
Evidence if HF and / or IHD

IHDA
Overweight and obese

Not achieving the target
No risk factors

Cost-effective
Patients at low risk of hypo

Evidence of insulin resistance

• low risk of hypoglycemia
• Extensive data on renal and CV protection in T2DM might be promising in PTDM
• Initial reduction in eGFR
• If used in TDM monitor renal function in the first 4 weeks

• Better HbA1c reduction
• Low risk of hypoglycemia
• Dose adjustment in low eGFR
• Data on renal and CV protection derived from type2 DM

• Limited safety and efficacy data.
• Low risk of hypoglycemia
• Adjust the dose with low eGFR except for Lixaglutin
• Limited data on renal and CV protection in PTDM

• increased risk of hypoglycemia
• Use cautiously in reduced eGFR

• Effective in PTDM
• Low risk of hypoglycemia
• Risk of fluid retention

3rd Line

Combination therapy of any of the classes. Avoid combining DPP4-I and GLP-1 analogs

4th Line

Consider adding insulin if not achieving targets. Insulin can be added earlier if HbA1c is >2% above target

Fig. 3. Suggested algorithm for management of post-transplant diabetes.
Management of Post-Transplant Diabetes

Diabetes mellitus is the leading cause of ESRD; preexisting diabetes or new diabetes post-transplant increases the risk post-transplantation. Prediction and correcting modifiable risk factors reduce the incidence and improve survival. Management includes manipulation of anti-rejection treatment, lifestyle adjustment, use of insulin in the early stages of hospital admission, and use of insulin with or without oral hypoglycemic agents in the outpatient setting. Transplant centers need to be equipped with specific protocols for detecting, diagnosing, and managing preexisting diabetes or PTDM.

Algorithm

As specific data on the safety and efficacy of specific oral hypoglycemic medications in post-transplant and PTDM is lacking, we suggest using insulin either intravenously or subcutaneously in the immediate postoperative period and during hospital admission for any intercurrent infection or rejection. For the outpatient setting, we suggest using oral medications with acceptable efficacy and a safety record (Fig. 2, 3).

Conclusion

Diabetes mellitus is the leading cause of ESRD; preexisting diabetes or new diabetes post-transplant increases the risk post-transplantation. Prediction and correcting modifiable risk factors reduce the incidence and improve survival. Management includes manipulation of anti-rejection treatment, lifestyle adjustment, use of insulin in the early stages of hospital admission, and use of insulin with or without oral hypoglycemic agents in the outpatient setting. Transplant centers need to be equipped with specific protocols for detecting, diagnosing, and managing preexisting diabetes or PTDM.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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