Post-transplantation Diabetes Mellitus

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Nomenclatures

Post transplantation diabetes mellitus (PTDM) was first described in kidney transplant recipients in 1964. 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) (1)

Several terms are used in the literature to describe the presence of diabetes following organ transplantation.

"New-onset diabetes after transplantation" (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant.

NODAT excludes patients with pretransplant diabetes that was undiagnosed, as well as post-transplant hyperglycemia that resolves by the time of discharge.

Another term, "post-transplantation diabetes mellitus" (PTDM), describes the presence of diabetes in the post-transplant setting irrespective of the timing of diabetes onset (2).

Utilizing the term NODAT is thought to be misleading because it seemingly excludes patients with undiagnosed pretransplant diabetes.

Factors that may lead to undiagnosed pretransplant diabetes include lack of universal pretransplant screening, impaired insulin clearance by the kidneys and/or impaired gluconeogenesis, and spuriously low A1C levels due to decreased red blood cell survival and chronic anemia (1).

At an expert meeting hosted in Vienna in 2013, the objectives were to update previous consensus statements, and secondly to debate deficiencies in the PTDM clinical evidence base (3).

Discussions that ensued led to 7 recommendations:

1) Change terminology from New-Onset Diabetes After Transplantation (NODAT) back to post-transplantation diabetes mellitus (PTDM).
2) Exclude transient post-transplantation hyperglycemia from PTDM diagnosis.
3) Expand screening tests for PTDM to incorporate postprandial (and evening) glucose monitoring and HbA1c to raise suspicion, while oral glucose tolerance tests remain the gold standard.
4) Identify patients at risk for PTDM.
5) Choose immunosuppression regimens so as to achieve the best outcome for patient and graft survival, irrespective of PTDM risk.
6) Adopt strategies for prevention and treatment beyond modification of immunosuppressive regimens.
7) Expand basic, translational, and clinical research in PTDM to address the areas of remaining controversy and speculation (3).

International consensus on post-transplantation DM

This meeting was endorsed by the European Renal Association (Diabesity Working Group) and the European Society for Organ Transplantation

(EKITA Working Group) & was held in Vienna in May 2022 (4).

Recommendations

Opinion Statement 1: Perform an oral glucose tolerance test for diagnosis and screening; start on the waiting list.
Opinion Statement 2: Be aware of the long-term consequences of prediabetes and PTDM.
Opinion Statement 3: Prioritize clinical attention to 'at risk' groups.
Opinion Statement 4: Consider the underlying Patho mechanism of PTDM development and the inter-relationship between β-cell dysfunction and metabolic stress.
Opinion Statement 5: Choose an immunosuppression regimen for optimization of patient and graft survival.
Opinion Statement 6: Emphasize lifestyle modification to all patients; consider medical or surgical intervention for treatment of obesity; use intermittent exogenous insulin intervention early post-transplantation for post-operative hyperglycemia.
Opinion Statement 7: Use the novel agents; personalize glucose-lowering therapy based upon a patient-dependent hierarchy.
Opinion Statement 8: Increase collaborative research between academic medicine, multi-disciplinary clinical teams, industry partners and patients (4).

Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of post-transplantation diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection.

The oral glucose tolerance test is the preferred test to make a diagnosis of post-transplantation diabetes mellitus.

Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of post-transplantation diabetes mellitus risk (2).

Incidence

There is considerable variation in the reported incidence of PTDM.
The reported rates of PTDM after kidney transplantation are 10–40%.
After heart transplantation, when OGTT has been used as the diagnostic criterion, the incidence has been reported at 20–28% at 5 years.
However, 5 years after liver transplantation, the incidence of PTDM is reported at almost 40%
PTDM after lung transplantation has an accumulated incidence of 20–40% (5).

Diagnosis of PTDM

Based on recent International Consensus Guidelines, the diagnosis of PTDM can be made using any of the following American Diabetes Association/World Health Organization criteria for the diagnosis of diabetes, once the transplant recipient has been discharged from the hospital and tapered to their maintenance immunosuppression. However, HbA1c should not be used alone to screen for the diagnosis of PTDM within the first year after transplant (6).

A) Fasting glucose >126 mg/dL (7 mmol/L) on more than one occasion.
B) Random glucose >200 mg/dL (11.1 mmol/L) with symptoms.
C) Two-hour glucose after a 75-g OGTT of >200 mg/dL (11.1 mmol/L).
D) HbA1c >6.5%.

Time post-transplant (days)	Diagnosis
0–45	Do not diagnose PTDM
46–365	OGTT Fasting glucose ≥ 126 mg/dl (≥ 7.0 mmol/l) and/or 2-h plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) Random glucose ≥ 200 mg/dl (≥ 11.1 mmol/l) HbA1c > 6.5% (48 mmol/mol): use cautiously as will underestimate PTDM, if used < 1 year post-transplant
> 365	OGTT HbA1c Fasting/random glucose

Table (1): Recommendations for screening and diagnosis of PTDM

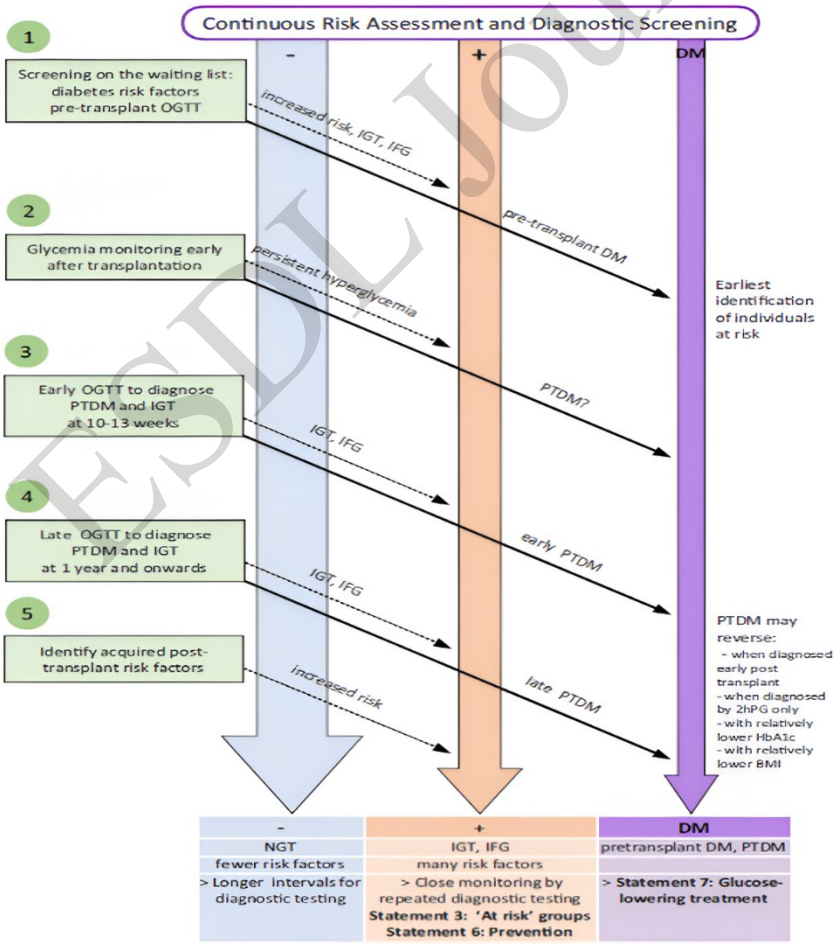


Figure (1): Five aspects of risk assessment for and diagnosis of PTDM and IGT
Adnan et al. Nephrology dialysis transplantation .2024 (4)

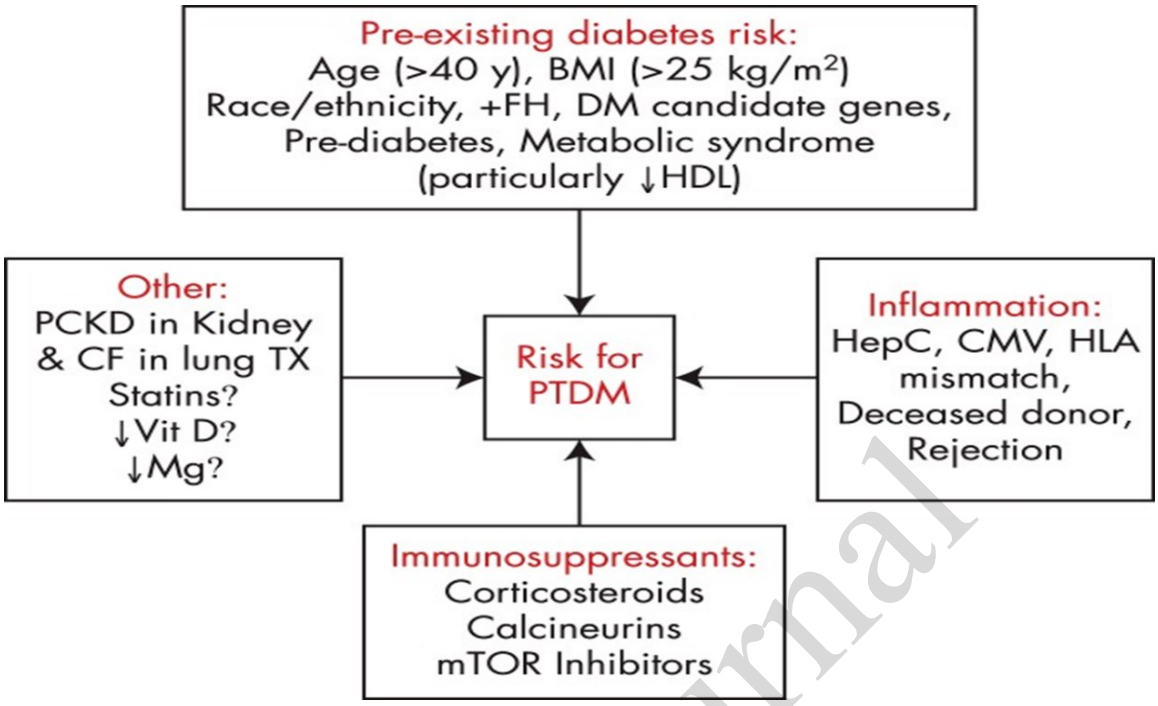


Figure (2): Risk factors and pathogenesis of PTDM
Shivasway ,Endocr Rev.2016(6)

Known and Potential Risk Factors

Just as with type 2 diabetes, PTDM is more likely to occur in individuals with pre-existing type 2 diabetes risk factors, including age and a family history of type 2 diabetes, and in those with race or ethnicity considered at high risk for type 2 diabetes.

Importantly, obesity, whether defined as elevated BMI or increased waist circumference, has also been associated with increased risk of type 2 diabetes as well as PTDM. Obesity can predate the transplant, but weight gain after transplant can also contribute (6).

Associated candidate genes

Some genes associated with risk of end-organ failure leading to solid organ transplant are also associated with risk of PTDM. Specifically, several retrospective studies have identified autosomal dominant polycystic kidney disease (PCKD) as increasing the risk of PTDM after kidney transplant.

Cystic fibrosis (CF) is a genetic disease that can lead to the need for a lung transplant. CF is also associated with a distinct type of diabetes, CF-related diabetes (CFRD). Thus, it is not surprising that those individuals with CF who have not developed CFRD before transplant are at higher risk for developing diabetes after lung transplant than other lung transplant candidates (6).

Potential role of "stress," inflammation, and infection

Acute and chronic systemic inflammation have long been shown to be risk factors for the development of type 2 diabetes.

Solid organ transplantation is, by definition, an inflammatory state because of ongoing graft-host response due to acute and/or chronic rejection, reduced renal function common in this setting, and

a high incidence of and/or chronic infections associated with immunosuppression (6).

Two infections in particular have been observed to contribute to PTDM risk.

One is the hepatitis C virus (HCV), well established to be associated with the risk of diabetes in nontransplant patients.

HCV has been consistently associated with an increased relative risk of PTDM (2.5- to 4-fold) after liver transplant.

Cytomegalovirus (CMV) is another infection associated with PTDM.

CMV infection is more common after transplant due to immunosuppression.

Several potential mechanisms for these CMV effects include CMV-induced or leukocyte-mediated damage or destruction of β-cells as well as proinflammatory cytokine production (6).

Corticosteroids are well established to cause hyperglycemia through several mechanisms:

by inducing or worsening pre-existing insulin resistance, increasing hepatic gluconeogenesis, and long-term, by stimulating appetite and weight gain.

The impact is dose-dependent.

High-dose corticosteroids, often used as part of induction protocols in the immediate post-transplant hospitalization, have a much greater impact than chronic low-dose corticosteroids that are common to many maintenance immunosuppression protocols (6).

Mycophenolate mofetil and azathioprine have not been shown to have a large impact on insulin action or glucose metabolism and so do not appear to have a major role in PTDM.

There is increasing evidence that the other commonly used immunosuppressants, particularly calcineurin inhibitors (CNIs) (eg, tacrolimus and cyclosporine) and inhibitors of the mammalian

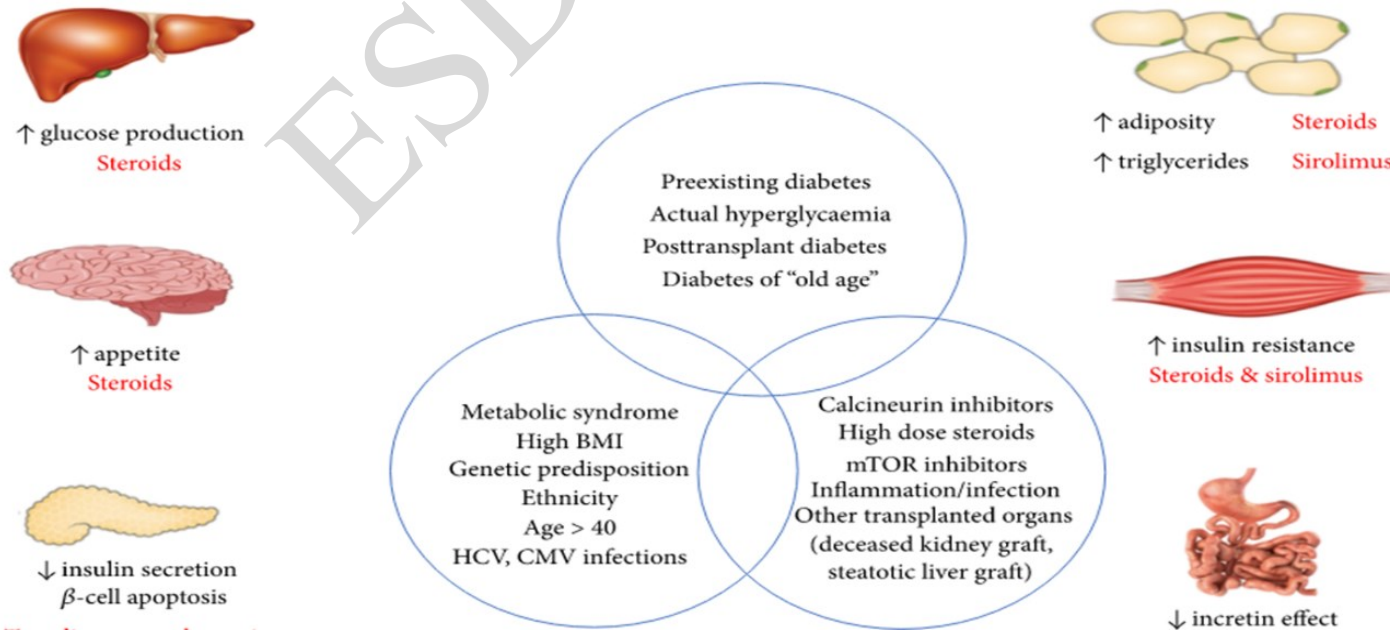


Figure (3): Role of immunosuppression agents
Matthew et al. Journal of transplantation .2018 (7)

target of rapamycin (mTOR; eg, sirolimus or rapamycin and everolimus), may contribute to PTDM (6).

Cyclosporine was the first CNI to be introduced, and it greatly improved graft survival with lower doses of corticosteroids.

Tacrolimus therapy increased diabetes risk in transplant recipients already known to be at the highest risk, such as African Americans and those with a prior history of hepatitis C.

Although tacrolimus appeared to increase the relative risk for developing PTDM more than cyclosporine treatment, it became apparent that cyclosporine was also associated with risk, 18% compared to 8%, respectively, based on data from the U.S. Renal Database for the 2-year incidence of PTDM after kidney transplant.

Tacrolimus was also shown to increase the incidence of prediabetes after kidney transplant (33% at 12 months) (6).

Studies performed predominantly in vitro and in animal models suggest that CNIs may increase the risk of PTDM by reducing insulin secretion, increasing insulin resistance through both insulin signaling and Tacrolimus was also shown to reduce β-cell mass and increase islet apoptosis, but it had less impact on insulin signaling, suggesting that its predominant action was on insulin production.

Increased apoptosis was also observed after 24-hour treatment of isolated human islets with tacrolimus through the up-regulation of caspase-3 cleavage and activity.

CNI treatment of animal models has also demonstrated decreased glucokinase activity and reduced insulin gene expression.

Another mechanism by which CNI has been suggested to contribute to hyperglycemia is hypomagnesemia.

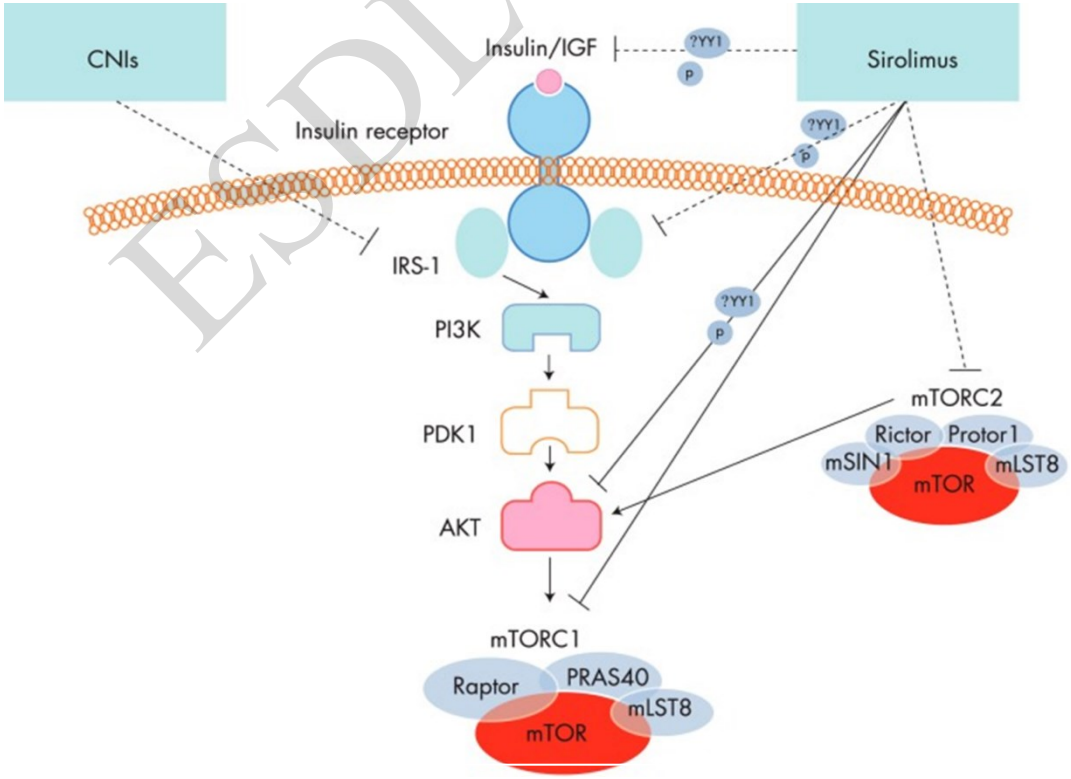


Figure (4): Mechanistic target of rapamycin (mTOR) signaling pathway
Shivasawy,Endocr Rev 2016 (6)

Hypomagnesemia alone is known to impact insulin signaling, is commonly associated with CNI treatment, and is associated with increased risk for PTDM (6).

Rapamycin is both an antiproliferative and a potent immunosuppressant.

It is produced commercially as sirolimus and its derivative, everolimus.

Early data suggested little or no diabetogenic effects of rapamycin, particularly in comparison with other immunosuppressants, and it was this that prompted its use in islet cell transplantation (8).

It was also for this reason that rapamycin has been promoted as a second-line therapy for recipients of solid organ transplants who have developed new-onset diabetes after transplantation (NODAT) while taking calcineurin inhibitors (CNIs).

However, there is an increasing view that rapamycin has profound effects on pancreatic β-cells, as well as altering insulin sensitivity.

Rapamycin inhibits mTOR, which, via mTORC1 and mTORC2, is part of complex signaling pathways controlling a host of important cellular functions, including mRNA translation, cell proliferation, cell growth, differentiation, protein synthesis, angiogenesis, and apoptosis (8).

Sirolimus binds to mTOR, and one of the important negative feedback mechanisms of this pathway is via protein kinase-dependent phosphorylation of IRS-1 at specific serine residues, leading to suppression of PI3K/Akt signaling (6).

Sirolimus treatment has been shown to reduce β-cell mass of human and rat islets through apoptosis.

Sirolimus also has antiproliferative effects on multiple cells.

It has also been shown to impair proliferation of pancreatic ductal cells, which some believe serve as a precursor for the development of new islets (6)

Indeed, the effects of sirolimus on glucose metabolism are not very clear.

Insulin receptor substrate-1 (IRS-1) and mTOR play a role in insulin signaling.

Early in-vitro studies suggest that it increases insulin responses in chronic insulin stimulation by inhibiting IRS-1 degradation. (8-10)

Contrary to this finding, more recent in-vitro studies showed that long-term mTOR inhibition impairs

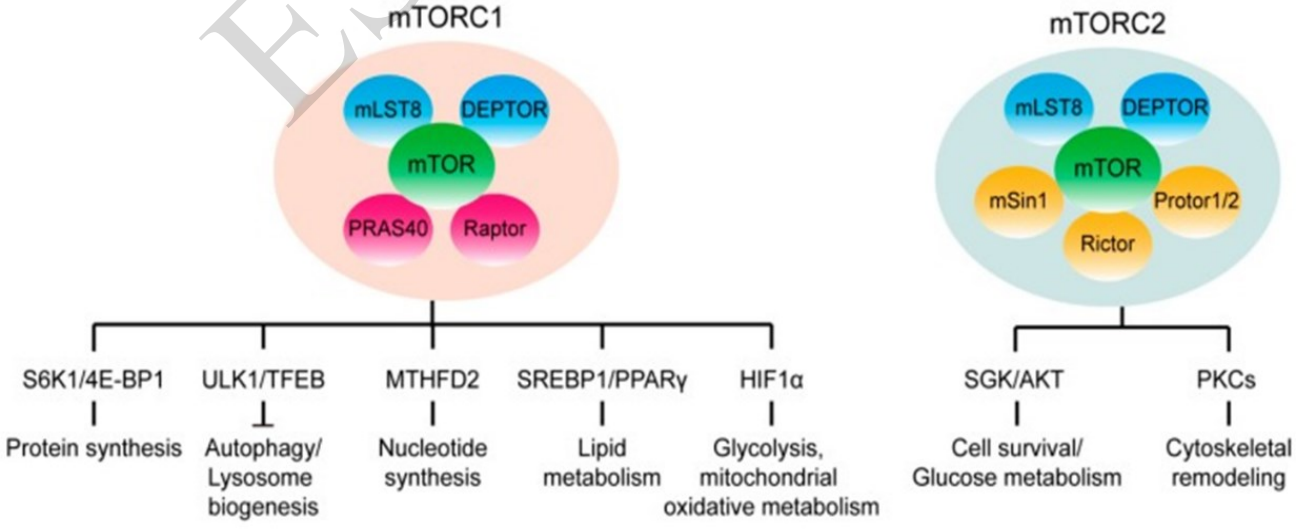


Figure (5): Composition and downstream functions of mTOR complexes.
Man et al .Int J Mol Sci .2018 (9)

activation of IRS-1 and AKT and augments insulin resistance and β- cell dysfunction.

Other possible mechanisms, by which sirolimus may cause NODAT, include impaired insulin-mediated suppression of hepatic glucose production, insulin resistance from ectopic triglyceride deposition or direct β-cell toxicity (10).

The antiproliferative agents, mycophenolate mofetil (MMF) and azathioprine, have not been shown to affect glucose metabolism or insulin action and do not appear to play a significant role in PTDM (7).

Treating Diabetes After Transplant

No studies to date have established which noninsulin agents are safest or most efficacious in PTDM.

The choice of agent is usually made based on the side effect profile of the medication and possible interactions with the patient's immunosuppression regimen.

Drug dose adjustments may be required because of decreases in the glomerular filtration rate, a relatively common complication in transplant patients (2).

A small short-term pilot study reported that metformin was safe to use in renal transplant recipients, but its safety has not been determined in other types of organ transplant.

Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials.

Thiazolidinediones have been used successfully in patients with liver and kidney transplants, but side effects include fluid retention, heart failure, and osteopenia.

Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in patients with PTDM are needed (2).

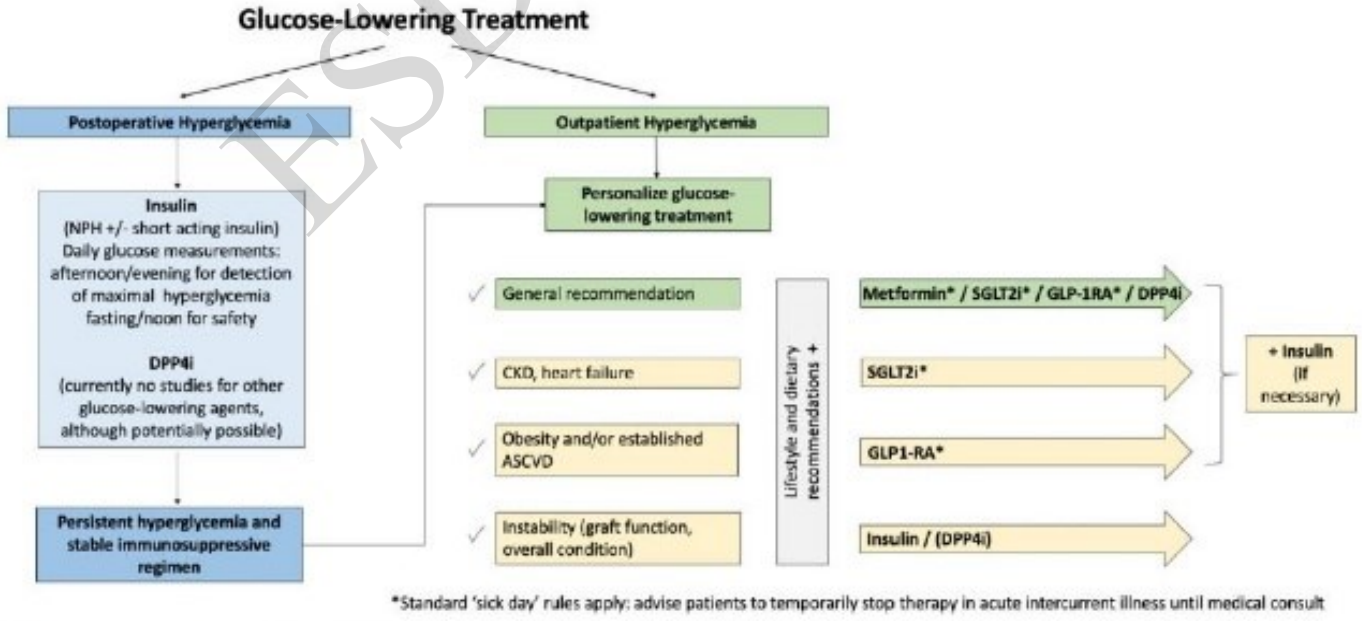


Figure (6): Glucose-lowering treatment: suggested algorithm.
Adnan et al. Nephrology Dialysis Transplanta 2024 (4)

Treatment of the hospitalized patient

Clinical Scenario	Concerns	Treatment Considerations	Potential Problems
Immediate post-transplant	High-dose immunosuppression, pain, and stress are common. Patient in ICU	Frequently require iv insulin infusion protocol. Hourly blood glucose monitoring initially	Requires frequent adjustment of insulin dose based on algorithm
First week post-transplant	Increased nutritional intake. Steroid doses weaning	High-dose immunosuppression common. Transition to sc insulin when stable and/or starting oral intake	Insulin requirements may change daily due to renal function changes, increased nutritional intake
Acute steroid bolus (eg, for acute rejection)	Increased insulin requirements	Consider basal bolus if very high-dose steroid, temporary iv insulin	consider temporary iv insulin
TPN or enteral feeding	Increased insulin requirements	Consider iv insulin as drip and/or in TPN bag	Adjust insulin dose for changes in TPN/tube feed rate or dextrose concentration

Table (2): Treatment of the hospitalized patient
Shivasway et al .Endocr Rev 2016 (6)

Outpatient glucose management

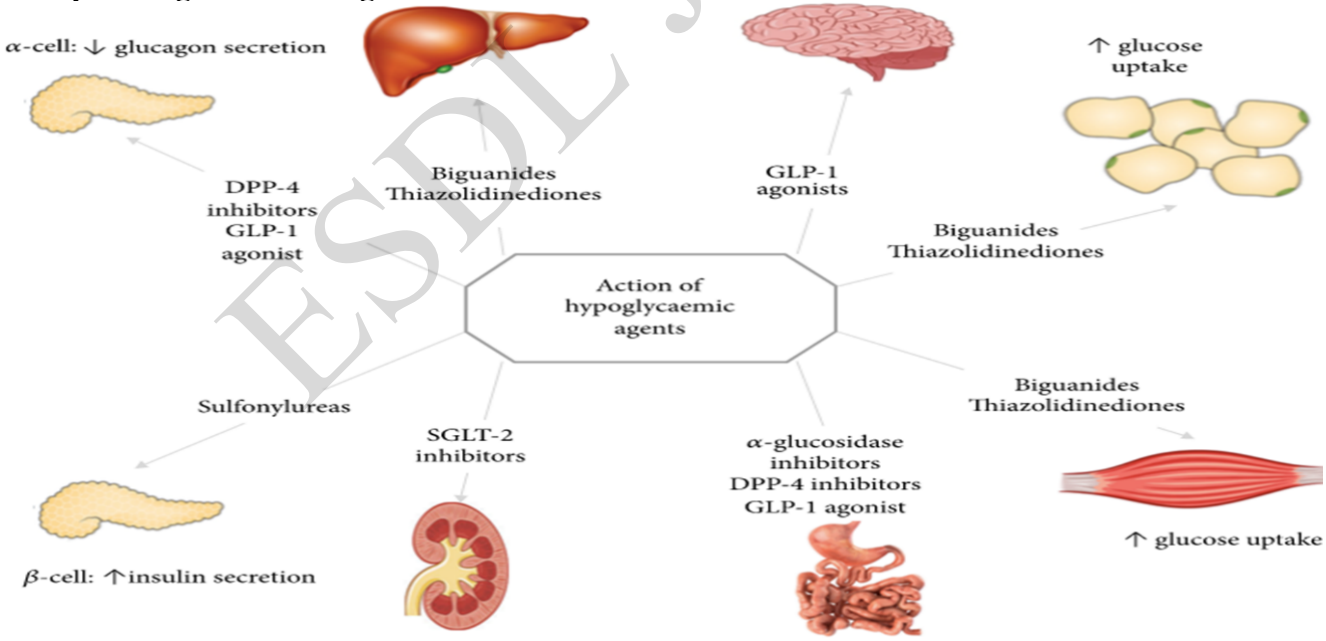


Figure (7): Action of Hypoglycaemic Agents
Matthew et al Endocr Rev 2016 (6)

Anti-Diabetic Agents in Organ Transplant Patients

Agent	Safety or Efficacy Studies in Transplant Patients	Potential Considerations in Organ Transplant Patient
Metformin	Effective in stable kidney transplant (KTX) patients but contraindicated for many other transplant (TX) groups, including during acute hospitalizations.	Should not be used during acute hospitalization, with ↓ GFR, ↑ LFTs, CHF, or active, significant infection; and should be held for planned IV contrast procedure.
Sulfonylureas	Efficacy is not well documented in transplant patients. Did not alter cyclosporine pharmacokinetics in a small study of KTX recipients with PTDM (Post-Transplant Diabetes Mellitus).	Increased risk of more frequent and more prolonged hypoglycemia with ↓ GFR.
Repaglinide	Effective and safe with no interaction with CNIs (Calcineurin Inhibitors) in a small study of KTX recipients with PTDM.	Less risk of hypoglycemia with ↓ GFR than sulfonylureas.
Thiazolidinediones (e.g., pioglitazone)	Effective and safe in small studies of KTX recipients.	Known risk for weight gain, edema, heart failure, and reduced bone mass; contraindicated with known elevated liver function tests (with the exception for known fatty liver disease including after liver transplant); contraindicated with known heart failure; unknown impact on risk for heart failure risk after transplant.
α-Glucosidase Inhibitors	No studies of safety or efficacy to date in organ transplant populations.	Avoid with ↓ GFR; unlikely to be an effective single agent.

GLP-1 Agonists (exenatide, liraglutide, lixisenatide)	Liraglutide did not affect tacrolimus concentration in a very small study of KTX recipients.	Decreases bowel motility, which may impact absorption of immune suppression agents and has not yet been studied; should not use if GFR < 40 mL/min.
DPP-4 Inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin)	Retrospective and small random controlled trials of KTX recipients show safety of several DPP-4 inhibitors.	Reduce dose of all but linagliptin with ↓ GFR.
SGLT-2 Inhibitors (dapagliflozin, canagliflozin, empagliflozin)	Known to increase risk of genitourinary infections in those with previous history, which is a concern in immunocompromised transplant patients; known to cause volume dehydration and hypotension, which may also be a concern in these patients as well as recent reports of diabetic ketoacidosis raise concerns of safety for most transplant populations.	Avoid until safety studies are performed.

Table (3): Anti-Diabetic Agents in Organ Transplant Patients

SGLT2 Inhibitors

There is presently no robust research evidence to support the use of SGLT2 inhibitors in PTDM.

In patients with heart transplants, empagliflozin was shown to produce a clinical reduction in body weight and blood pressure and a nonsignificant reduction in HbA1c. After 147 cumulative months of empagliflozin use, no adverse events such as diabetic ketoacidosis (DKA) or genitourinary infections were reported.

They are promising agents because of specific benefits, i.e. weight loss, low risk of hypoglycaemia, renoprotection, cardio protection, and reduction in incidence and admissions with heart failure.

They cannot be initiated in patients with an eGFR<60 ml/min/1.73 m2 and should be discontinued when eGFR<45 ml/min/1.73 m2.

No clinically meaningful interaction was noted between cyclosporine and canagliflozin in healthy participants (5).

Long-Acting Dual GIP and GLP-1 Receptor Agonist Tirzepatide is a new therapeutic compound with proven efficacy in maintaining normal glycemia in patients with DMT2.

It is a dual GIP and GLP-1 receptor agonist & its mechanism of action involves activation of the GLP-1 signaling pathway, which mobilizes glucose-dependent insulin secretion through GIP receptor activity. The drug also has a long half-life,

So the time during which blood glucose levels remain within a safe range—71–140 mg/dL—is extended. In addition, it increases the sensitivity of pancreatic β-cells to glucose, due to the fact that it enhances first- and second-phase secretion in a glucose-dependent manner (12).

New Directions in the Treatment of Diabetes Mellitus

1. Glucokinase Activators

Glucokinase activators (GKAs) are a class of antidiabetic drugs developed to regulate blood glucose levels and improve β-cell function in diabetic patients.

Glucokinase, also known as hexokinase IV, is a key enzyme present mainly in the liver and pancreatic β-cells.

In β-cells, it acts as a glucose sensor, initiating glucose phosphorylation, which leads to ATP production and inhibition of ATP-sensitive K+ channels.

This, in turn, opens calcium channels, promoting insulin release. In the liver, glucokinase acts as a "gatekeeper" for cells, where glucose phosphorylation culminates in glycogen synthesis (12).

2. Imeglimin

The investigational drug imeglimin, representing a new pharmaceutical group called

"glimin", stands out for its innovative mechanism of action compared to other medications. It positively affects insulin sensitivity and reverses pancreatic β-cell dysfunction. Studies have confirmed that imeglimin exhibits potent anti-diabetic effects, normalizing glucose homeostasis by acting on various metabolic pathways. The key effects of imeglimin include improved insulin sensitivity through potential effects on glucose transporter-4 (Glut-4) and insulin receptor autophosphorylation.

In addition, imeglimin has antiapoptotic effects, stimulating pancreatic β-cell function in patients with DMT2. It also reduces hepatic

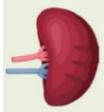
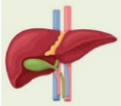
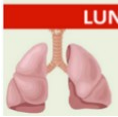
		DIRECT EFFECTS ON ORGANS		INDIRECT EFFECTS ON ORGANS	
		SGLT2 inhibitors	GLP1R agonists	SGLT2 inhibitors	GLP1R agonists
KIDNEY TRANSPLANT RECIPIENTS			**KIDNEY**		
	*PTDM risk: 10-20% [REFs 3-5]. Increased risk of mortality. Graft loss is a challenge.* **Opinion:** Use SGLT2i as add-on, monitor glucosuria ketonuria, UTI by urinary dipstick tests. GLP1-RA for ↑BMI patients, ideal in poor glycemic control. Study monotherapy!	↑ natriuresis → restoration of TGF → intraglomerular pressure ↓ → albuminuria ↓	↑ natriuresis (potentially similar as with SGLT2i, but less potent, [renal endpoints in studies all driven by albuminuria]) ↓ glomerular pressure ↓ inflammation ↓ albuminuria	↓ glucose ↑ ketones (↑ glucagon) ↓ vascular rigidity ↓ uric acid ↑ HIF-1	↑ utilization of glucose (and potentially of other macronutrients, prandially)
HEART TRANSPLANT RECIPIENTS			**HEART & CV-SYSTEM**		
	*PTDM risk: 20-30% [REF 6]. Increased risk of mortality.* **Opinion:** Safety suggested from retrospective studies. SGLT2is and GLP1-RAs could be even more attractive than for kidney transplant recipients (better eGFR; UTIs no major concern, potential CV risk reduction). ↑BMI patients: GLP1-RAs first. Study prospectively!	Speculative. (SGLT2 is not expressed in the heart [only SGLT1.]) However, direct effects of SGLT2is on the heart have been described [REF 123]	↑ heart rate (but does not appear to increase cardiovascular risk [REF 141])	↓ glucose ↑ ketones (↑ glucagon) ↓ insulin resistance ↓ uric acid ↓ weight & BP ↓ visceral fat ↓ arterial stiffness ↓ plasma volume	↑ utilization of glucose (and potentially of other macronutrients, prandially) ↓ weight ↓ blood pressure ↑ cardiac output ↑ vasodilation ↓ fatty acid metabolism
LIVER TRANSPLANT RECIPIENTS			**LIVER**		
	*PTDM risk: 20-40% [REFs 7-11]. Increased risk of mortality.* **Opinion:** No data available for SGLT2is, but SGLT2is & GLP1-RAs very attractive. Study prospectively!	Speculative. (SGLT2 is not expressed in the liver; direct effects of SGLT2is have not been described.)	↓ steatosis ↓ VLDL (ApoB100) ↓ glucose production ↓ inflammation Direct benefit? [REF 144]	↓ glucose ↑ glucagon ↑ hepatic glucose production (↑ SNS)	↑ utilization of glucose (and potentially of other macronutrients, prandially)
LUNG TRANSPLANT RECIPIENTS			**LUNG**		
	*PTDM risk: 20-40% [REFs 12, 13]. Increased risk of mortality.* **Opinion:** Attractive, study prospectively! (no data)	Speculative. (SGLT2 is not expressed in the lung. See also above.)	↓ inflammation Direct benefit? [REF 144]	↓ glucose ↑ ketones (↑ glucagon)	↑ utilization of glucose (and potentially of other macronutrients, prandially)

Table (4): Potential Benefits of SGLT2 Inhibitors and GLP1-Ras in Solid Organ Transplant Patients
Transplant International, volume 34 .2020 (11)

gluconeogenesis by reducing phosphoenolpyruvate and glucose-6-phosphatase activities in hepatocytes, while improving mitochondrial function and regulating intracellular energy production. Imeglimin is also important for pancreatic function, stimulating insulin secretion and increasing cellular Nicotinamide Adenine Dinucleotide (NAD+) levels and calcium ion mobilization, resulting in better insulin exocytosis efficiency.

Moreover, imeglimin exhibits antioxidant activity by inhibiting the production of reactive oxygen species in the mitochondria. The pharmacokinetics of imeglimin suggest efficacy in lowering glycated hemoglobin (HbA1c) levels within 16 weeks of treatment (12).

3. Pramlintide

Pramlintide is an analog of amylin, a hormone produced by the β-cells of the pancreas that works with insulin to regulate blood glucose levels, especially after meals. It is an antidiabetic drug used to treat DMT1 and DMT2 in patients who also use insulin for meals and have problems with blood glucose control. Pramlintide works by slowing gastric emptying, which helps control glucose levels after a meal.

Pramlintide is administered as an injection (subcutaneous injection) and is usually administered in combination with insulin before meals. It is important that patients carefully monitor their blood glucose levels to avoid hypoglycemia, especially at the beginning of treatment (12).

Drug-drug interactions between immunosuppressants and antidiabetic drugs in the treatment of post-transplant diabetes mellitus

Cyclosporine (CsA) itself inhibits the cytochrome P450 (CYP) 3A4 enzyme and a variety of drug transporters.

It increases exposure to repaglinide, sitagliptin, nateglinide, glyburide, saxagliptin, vildagliptin and alogliptin, gliptin and several sodium-glucose transporter (SGLT)-2 inhibitors.

Available data, although limited, suggest that these increases are modest and, particularly with regard to gliptins and SGLT-2 inhibitors, unlikely to result in hypoglycemia.

The interaction with repaglinide is more pronounced but does not preclude concomitant use if the repaglinide dose is gradually titrated (13).

Although CNIs and mTORi are intrinsically prone to DDIs, their disposition is not influenced by metformin, pioglitazone, sulfonylureas (except possibly glyburide) or insulin.

An effect of gliptins on the disposition of CNIs and mTORi is unlikely, but has not been definitively ruled out.

Based on their disposition profiles, glyburide and canagliflozin could affect CNI and mTORi disposition, although this requires further study.

Finally, delayed gastric emptying as a result of glucagon-like peptide-1 agonists seems to have a limited, but not necessarily negligible effect on CNI disposition.

Mycophenolate mofetil and azathioprine do not engage in DDIs with any antidiabetic drug (11-12-13).

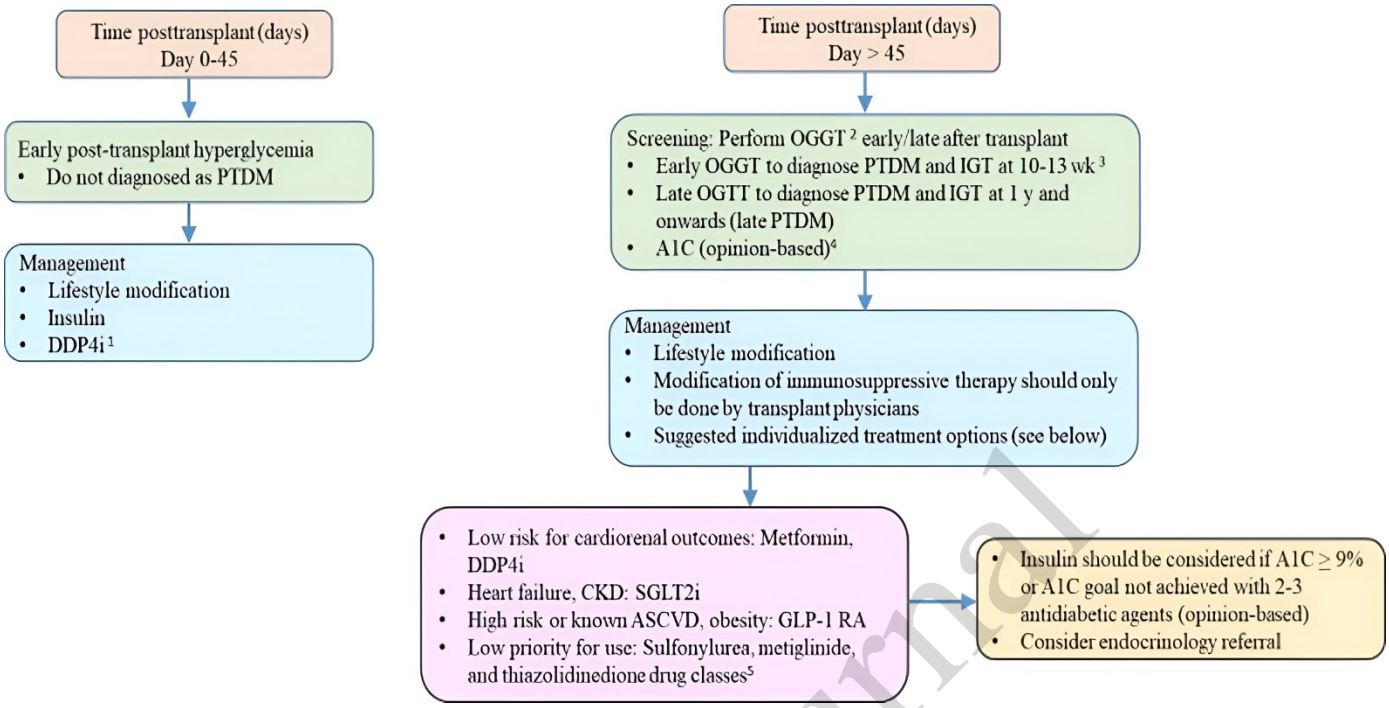


Figure (8): Suggested screening and diagnosis of early post-transplant hyperglycemia and PTDM (based in part on the 2024 international consensus guidelines).Pham et al . Endotext 2025 (1)

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