Post Transplant Diabetes Mellitus

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Introduction

- Common: PTDM affects 20–30% of renal transplant recipients.
- Severe: The development of PTDM is associated with 67% increased risk of graft failure and an 87% increased risk of death due to premature CVD, cardiovascular deaths and infections
- Worse results are seen in those recipients with previous DM

- Should be actively screened for in all transplant recipients, and actively managed with structured education, screening for complications, cardiovascular risk reduction and anti-hyperglycaemic therapy.

Hecking M, et al. Management of posttransplant diabetes: Immunosuppression, early prevention, and novel antidiabetics. Transpl Int 2021; 34: 27–48

Introduction

- PTDM is more common among liver than kidney transplant recipients.
- In one study, using the same immunosuppressants in both types of solid transplant recipients:
  - The incidence of PTDM was much higher in individuals receiving a liver rather than those receiving a kidney transplant (30% vs.19%), respectively.
- Most patients with PTDM are asymptomatic, Symptoms are the same as in non-transplant DM patients.

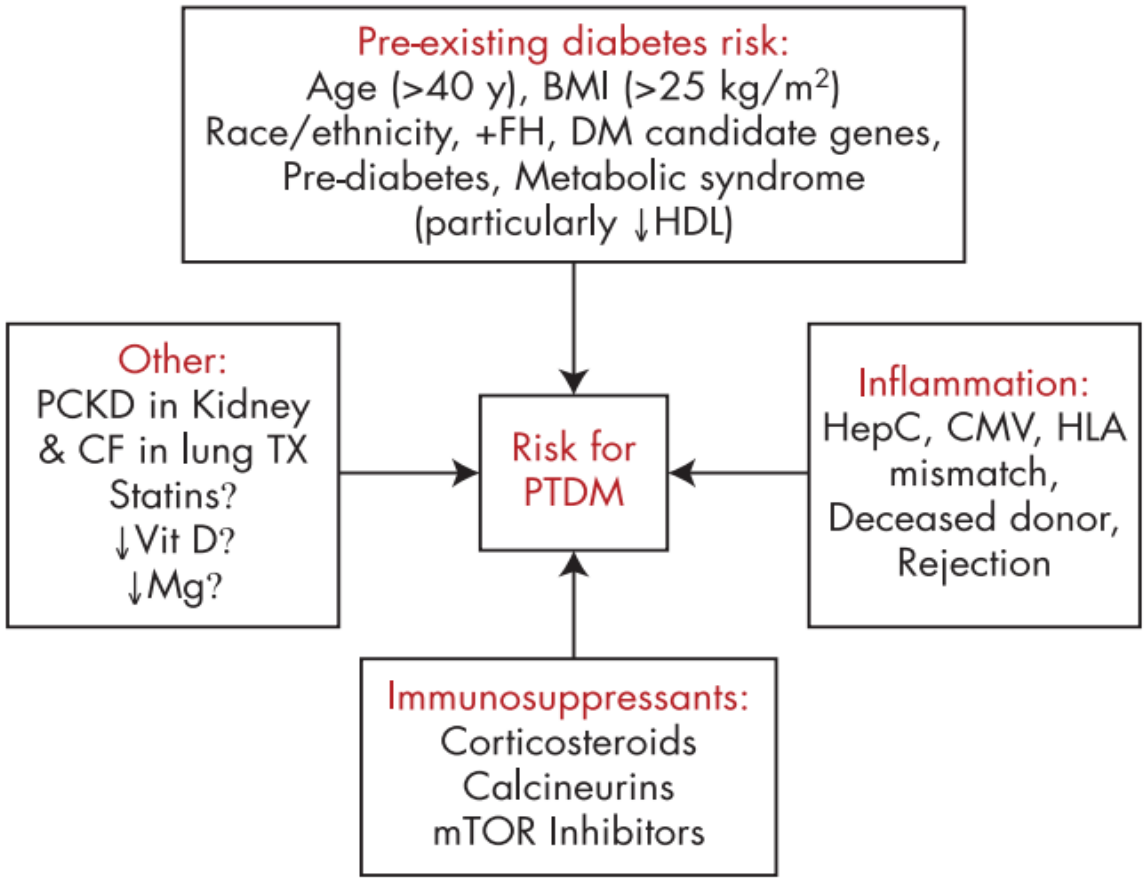
Incidence Per Transplanted Organ

Table 1 | **Characteristics of PTDM according to transplanted organ**

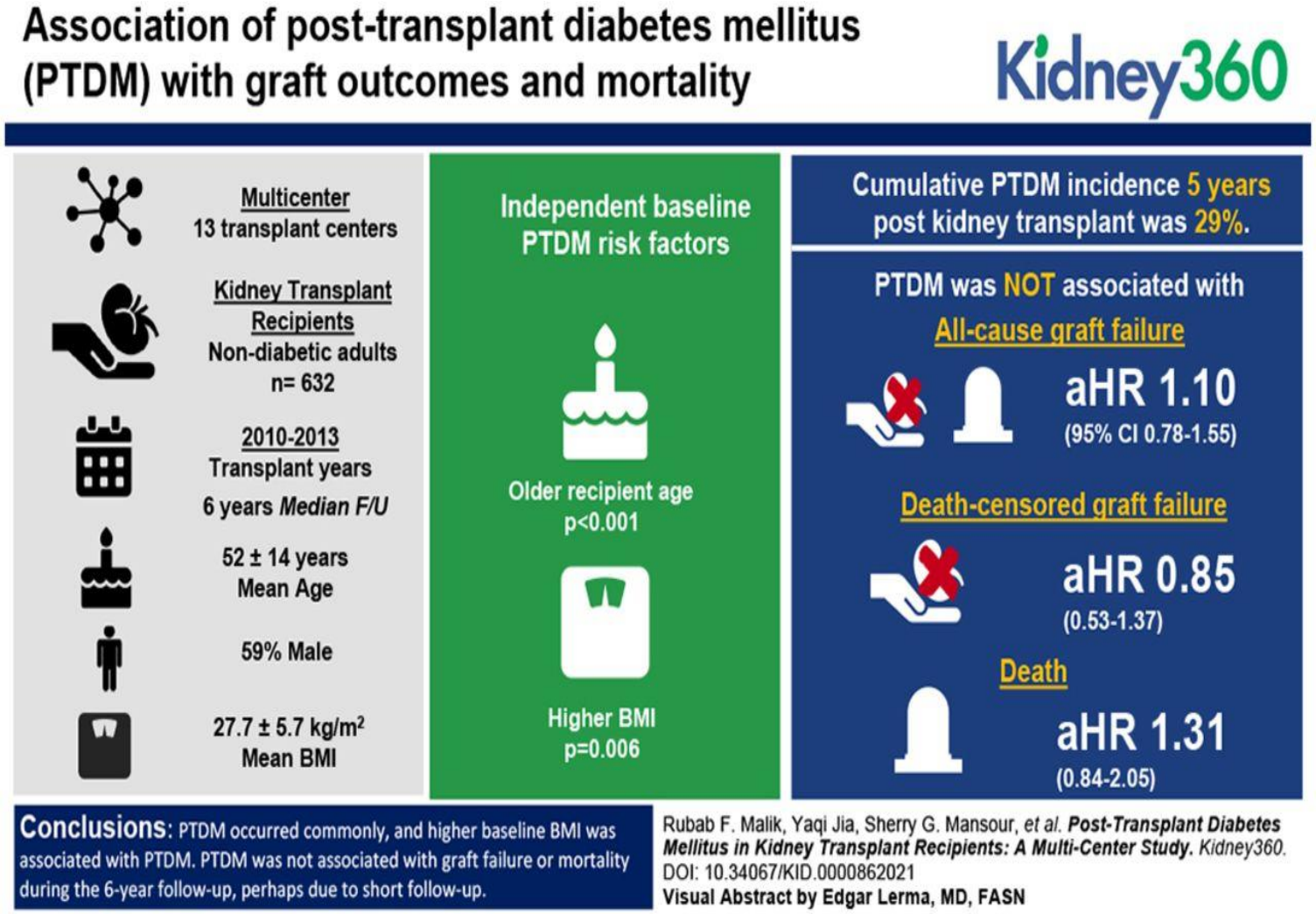
Organ	Average accumulated incidence (%)	Evidence for association to mortality	Diagnosis at risk of PTDM	Refs
Kidney	10–20	++	Autosomal dominant polycystic kidney disease	8,22,98
Liver	30–40[a]	+	Nonalcoholic steatohepatitis, HCV infection with cirrhosis[b]	15
Heart	20–30	+	None	12
Lung	20–40	+	Cystic fibrosis	13,122

+, some evidence; + +, extensive evidence; HCV, hepatitis C virus; PTDM, post-transplant diabetes mellitus. [a]Incidence might be lower in cohorts of people of Asian origin[108,110]. [b]HCV is also an acknowledged risk factor for PTDM in other organ transplants.

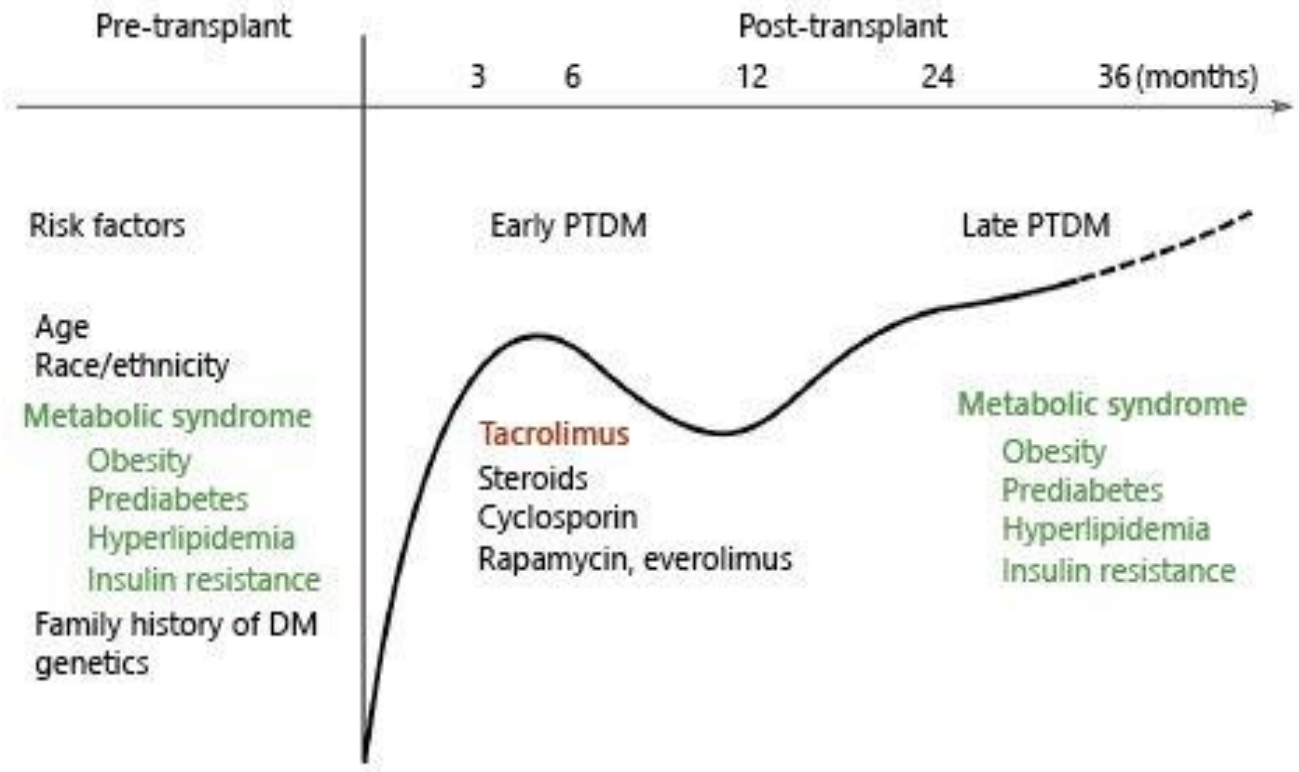
Risk Factors



Association with Graft Outcome



Timeline of Risk Factors for PTDM



Corticosteroids

- Traditionally associated with hyperglycemia and DM.
- The diabetogenic effect of corticosteroids is related to both the dosage and the duration of therapy.
- Post-transplant steroid therapy increases the risk of PTDM by 42% while steroid free regimens reduce the risk to less than 10%.
- Induce PTDM through:

  Inhibiting pancreatic insulin production and secretion.

  Decreasing peripheral insulin sensitivity.

  Increasing hepatic gluconeogenesis.

  Promoting protein degradation to free amino acids in muscles.

Calcineurin inhibitors (CNI)

- Given to most transplant recipients and are associated with hyperglycemia.
- CNIs cause hyperglycemia by:

✓ Reducing the number of Glucose Transporter Type 4 (GLUT-4) receptor molecules on the adipocytes, this leads to a reduction of glucose uptake.

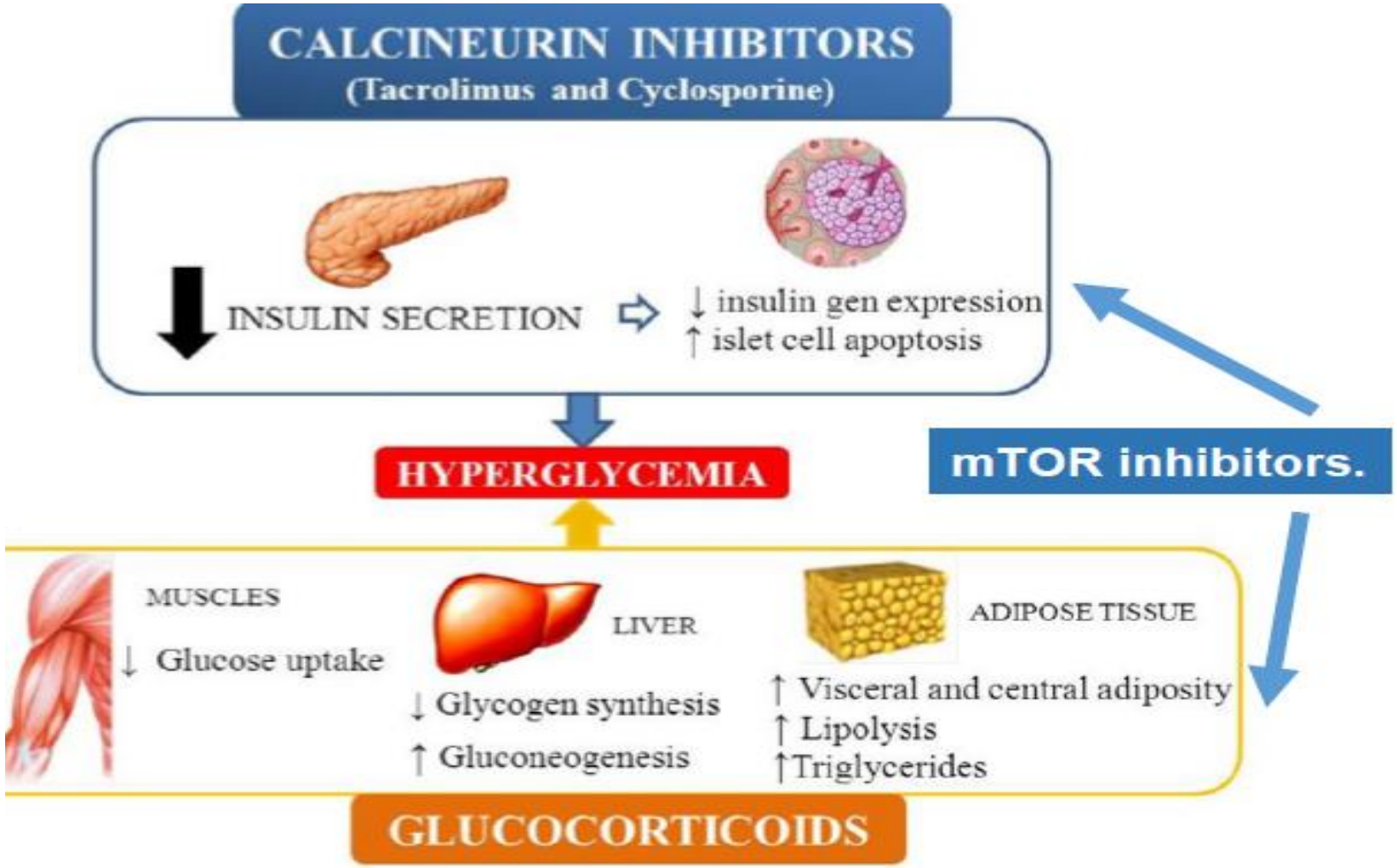
✓ Decrease the pancreatic beta-cell density by interfering with the activated T-cell signaling in pancreatic beta-cells.

- Studies report that the incidence of PTDM is significantly higher in patients who are treated with tacrolimus compared to those who have had therapy with cyclosporine.
- The effect of tacrolimus in the development of glucose intolerance is reversible with drug discontinuation.

Other Medications

- Sirolimus is another immunosuppressant that has been associated with PTDM, especially when used in combination with CNI.
- There is no known recognized association between mycophenolate mofetil and azathioprine use and the development of PTDM.

Immunosuppression



Immunosuppression

	Post-transplant diabetes	Lipids	Blood pressure	GFR	Proteinuria	Weight gain
Corticosteroids*	Increased	Increased	Increased	"	"	Greatly increased
Tacrolimus*	Increased	Slightly increased	Increased	Slightly decreased	"	"
Ciclosporin*	Slightly increased	Increased	Greatly increased	Slightly decreased	"	"
mTORi*	Slightly increased	Greatly increased	"	"	Slightly increased	"
Mycophenolic acid*	"	"	"	"	"	"
Azathioprine*	"	"	"	"	"	"
Belatacept*	Slightly decreased?	Slightly decreased?	Slightly decreased?	"	"	"
Basiliximab†	Slightly increased?	"	"	"	"	"
Monoclonals†	"	"	"	"	"	"

GFR=estimated glomerular filtration rate. *Maintenance immunosuppression. †Induction therapy. ? indicates insufficient evidence.

Diagnosis of PTDM

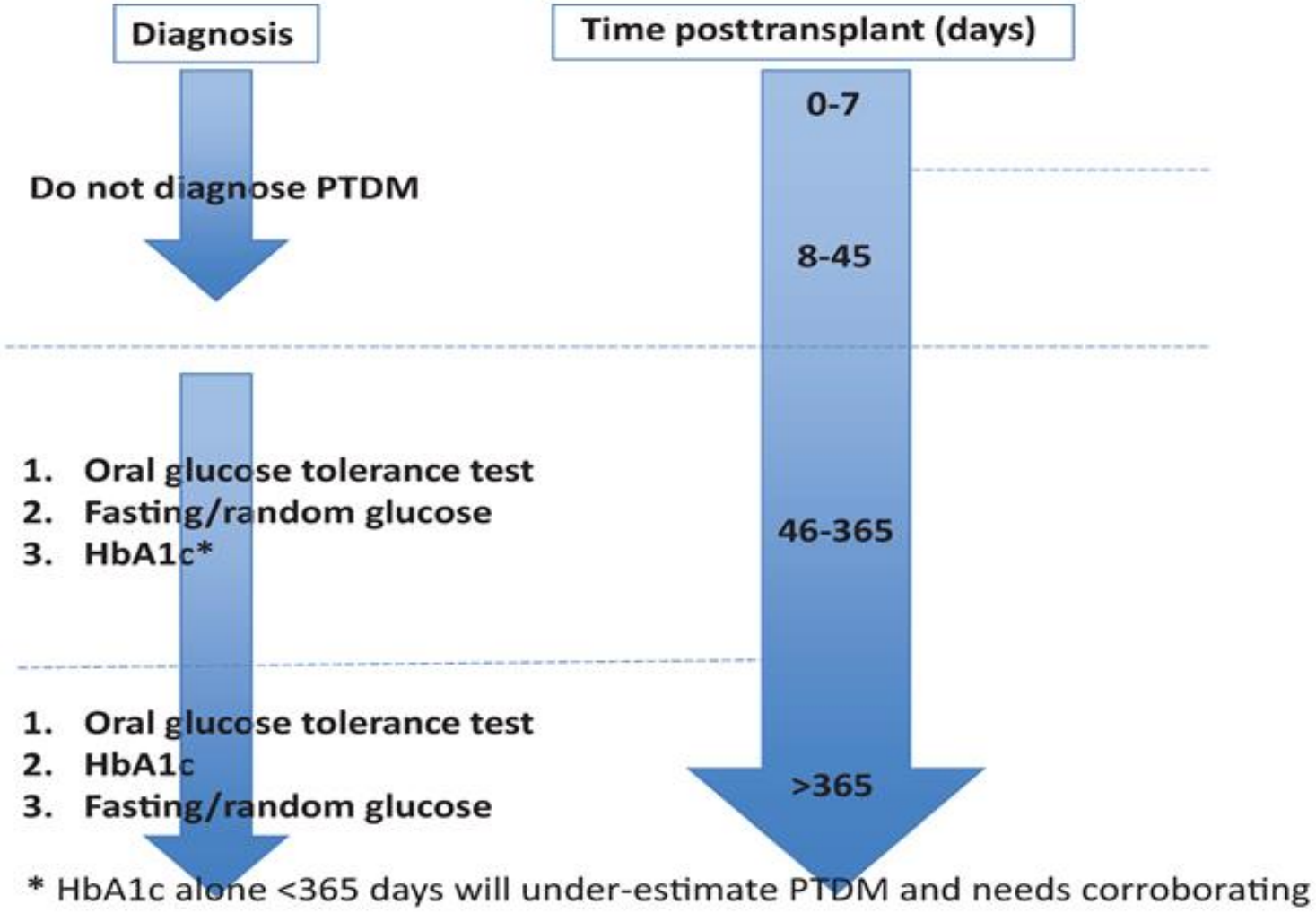
- The criteria for diagnosing PTDM are based on those used for T2DM in the general population (ADA 2021, WHO).
- Transient Post-Operative Hyperglycaemia Is Not PTDM , it occurs in 80% of the patients early after surgery, commonly related to perioperative stress, but must be taken into account since it is associated with future development of the disease.
- The diagnosis of PTDM should be made in clinically stable patients, far from the perioperative period by at least 6 weeks.
- HbA1c is unreliable in diagnosing PTDM specially in the early post operative period since it is affected by anemia, Erythropoietin use and blood transfusion.

Criteria for Diagnosis

Diabetes	
RPG	≥200 mg/dL (11.1 mmol/L)
FPG	≥126 mg/dL (7 mmol/L)
2hPG	≥200 mg/dL (11.1 mmol/L)
HbA1c	≥6.5%
Prediabetes	
IFG	FPG 100–126 mg/dL (5.6–6.9 mmol/L)
IGT	FPG <126 mg/dL (7 mmol/L) 2hPG 140–200 mg/dL (7.8–11 mmol/L)
Increased risk of diabetes	HbA1c 5.7–6.4%
Normal glucose tolerance	FPG <100 mg/dL (5.6 mmol/L) 2hPG <140 mg/dL (7.8 mmol/L) HbA1c <5.7%

ADA, American Diabetes Association; RPG, random plasma glucose; FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose after an oral glucose; IFG, Impaired fasting glucose; IGT, impaired glucose tolerance.

Diagnosis

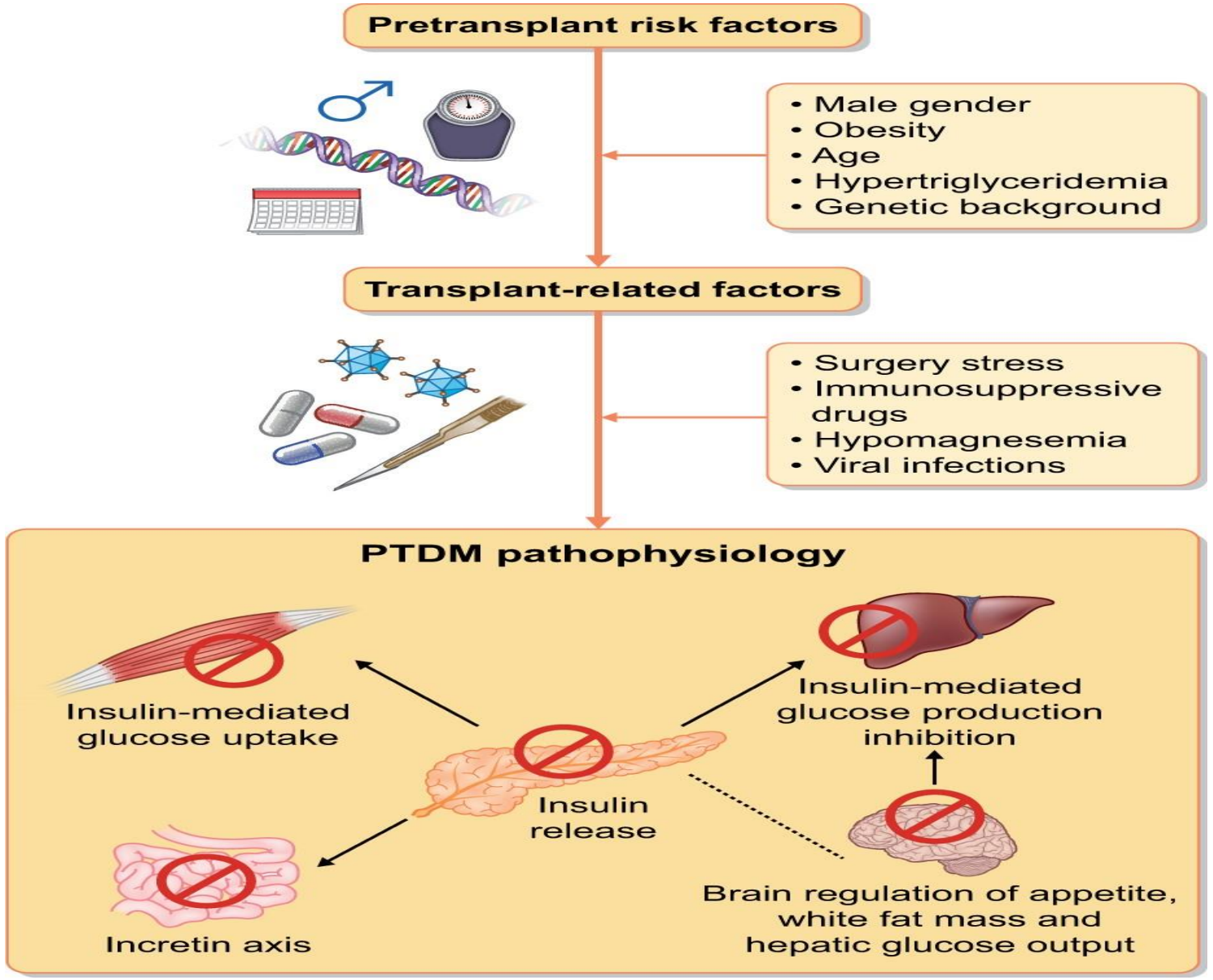


* HbA1c alone <365 days will under-estimate PTDM and needs corroborating

Pathophysiology of PTDM

- ß-cell damage and dysfunctional insulin release.
- Impaired insulin-mediated glucose uptake in the peripheral tissue.
- Impaired insulin-mediated suppression of hepatic glucose output secondary to disability of the incretin axis between the gut and pancreas.
- Impairment of brain regulation of the appetite, white fat mass and hepatic glucose output.

Pathophysiology of PTDM.



Clin Kidney J, Volume 15, Issue 1, January 2022, Pages 5–13,https://doi.org/10.1093/ckj/sfab131

Clinical Evolution of PTDM and Prediabetes

- **Early PTDM:**

✓ Most cases of PTDM (about 70–80%) are observed early after transplantation, that is, 3–6 months.

✓ 20–30% of early PTDM may revert into normal or prediabetes in the following months.

- **Late PTDM:**

✓ Develop during follow-up, from 12 months onwards.

✓ The annual incidence of *late PTDM* is similar to that observed in patients with prediabetes in the general population, ~7%

✓ During follow-up, prediabetes may persist in about 40%, normalize in 40%, or evolve into PTDM (late PTDM) in 20% of recipients.

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Diabetes Care

WWW.DIABETES.ORG/DIABETESCARE
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AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2021

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Classification

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune ß-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a progressive loss of ß-cell insulin secretion frequently on the background of insulin resistance)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use) or **after organ transplantation.**
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

Post-transplantation Diabetes Mellitus

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

2.20 The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. B

2.21 Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. E

Differential Diagnosis

	Type 1 diabetes	Type 2 diabetes	Post-transplant diabetes
Pathophysiology	Insulin deficiency due to loss of pancreatic β cells (immune mediated or idiopathic)	Insulin resistance with or without relatively reduced insulin secretion	Pancreatic β-cell dysfunction in presence of insulin resistance
Primary pathophysiological defect	Pancreatic β cell insufficiency	Insulin resistance	Pancreatic β-cell dysfunction
Exogenous insulin need	Essential	Might be needed	Very likely early, might be needed later
Age of onset	Younger than 40 years	Older than 40 years	Any age, but age increases risk
Affected by lifestyle	No	Yes	Yes, but many transplant-specific confounders
Ketoacidosis risk	Common	Very rare	Rare
Auto-antibodies	Present	Absent	Absent

Management of PTDM

- Early Prevention
- Glycemic Goals.
- Life Style
- Immunosuppression.
- Drug Therapy

The new guidance from the Association of British Clinical Diabetologists and the Renal Association (Chowdhury et al, 2021).

- PTDM should not be diagnosed within 3 months of transplantation.
- The optimum screening method for postoperative hyperglycaemia is the use of afternoon capillary blood glucose (CBG) measurements.
- If hyperglycaemia is significant and persistent (two CBG measurements >200 mg/dL), treatment should be initiated.
- If glucose readings are above 252 mg/dL on two occasions, insulin therapy is advocated,
- At 3 months postoperatively, most patients are on stable immunosuppression doses and, therefore, can be screened for PTDM using oral glucose tolerance test.

Preoprative

- Establish risk factors for diabetes (obesity, family history, previous DM, high-risk ethnic group, glucocorticoid therapy).
- Monitor FPG and HbA1c ideally 6-monthly:

  High risk if FPG 110–125 mg/dL or HbA1c 6.1–6.4%.
- If high risk of diabetes, advise weight loss, increased exercise improved diet and smoking cessation.
- If HbA1c > 6.5% or FPG >126 mg/L on two occasions, diagnose diabetes and put on to standard diabetes pathway.

Immediate Postoprative

- Monitor afternoon CBG readings.
- If CBG persistently (two readings) >200 mg/dL, consider therapy.
- If CBG 200–250 mg/dL and patient is eating and clinically well, consider oral hypoglycaemic therapy (metformin [if eGFR >30 mL/min/1.73 m2], DPP-4 inhibitor or sulfonylurea, alone or in combination, may be used).
- If CBG >250 mg/dL on two occasions, commence insulin therapy.

Up to 6 Weeks Postoperative

- Regular review with aim to reduce glucocorticoid dose, stabilize immunosuppression and consider conversion to less diabetogenic CNI therapy (e.g. cyclosporine) if no signs of rejection and graft function is stable.
- Reduce oral hypoglycemic therapy or insulin if possible.
- Ensure diet and lifestyle changes are optimized.
- At 6 weeks, consider OGTT if practical.
- During OGTT, if FPG >126 mg/dL or 2-hour glucose >200 mg/dL, diagnose PTDM and treat as below.

3 Months Postoperative

- If CBG well controlled and HbA1c at target, consider reduction in anti-hyperglycaemic therapy with careful self-monitoring of CBG.
- If hyperglycaemia resolved (CBG <200 mg/dL) and off anti-hyperglycaemic therapy, screen for PTDM with OGTT if possible;
- if not, request HbA1c and FPG:

- If HbA1c >6.5% or FPG >126 mg/dL on two occasions, diagnose PTDM.
- Refer patient for structured education and regular screening of eyes, feet, kidneys, blood pressure, weight, smoking status and lipids.
- Manage cardiovascular risk factors.
- Individualize glycaemic target according to patient's preference and comorbidities.
- Drugs such as metformin (if eGFR >30 mL/min/1.73 m2), DPP-4 inhibitors, GLP-1 receptor agonists and insulin can all be used safely post-transplantation.
- Avoid pioglitazone and saxagliptin in heart failure.
- Seek specialist advice when considering SGLT2 inhibitors.

- If HbA1c <6.0% and FPG <100 m/dL, PTDM is not diagnosed Continue to monitor HbA1c and FPG at 12 months and then annually.
- If HbA1c 6.0–6.4% or FPG 100–126 mg/dL, patient is at risk of developing PTDM.
- Continue to monitor HbA1c and FPG at 6-monthly intervals.
- Offer lifestyle advice to reduce risk of developing PTDM.

Glycemic Goals

6.5a An A1C goal for many adults of <7%(53 mmol/mol) without significant hypoglycemia is appropriate. A

6.6 On the basis of provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable, and even beneficial, if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. C

ADA 2021

Glycemic Goals (continued)

6.7 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy, or where the harms of treatment are greater than the benefits. B

6.8 Reassess glycemic targets over time based on the criteria in Fig. **6.2** and in older adults (**Table 12.1**). E

ADA 2021

Management of PTDM: Immunosuppression

- **CNIs :** Strategies to minimize or avoid CNIs exposure have been shown to reduce the odds of developing PTDM in a meta-analysis of 56 randomized controlled trials (with concomitant superior overall graft survival).

  Consider Cyclosporin in diabetic patients or high PTDM risk.

- **Steroids :** Controversy remains within the transplant community with regards to corticosteroid avoidance (defined as complete avoidance or withdrawal within the first days kidney transplantation) or corticosteroid withdrawal (defined as discontinuation at a certain time point in the later post-transplant phase) as potential strategies to attenuate the risk of PTDM.
- **Induction therapy :** one study reported a reduction in PTDM incidence with alemtuzumab compared to IL2 receptor antagonists, can be explained by lower doses of steroids and CNIs with induction.

Glucagon Like Peptide-1 Receptor Agonists (GLP1-RA)

- In case of PTDM, GLP-1 RAs have the following potential benefits:

✓ Metabolic impact: increases insulin secretion and reduces glucagon secretion.

✓ Cardiovascular effects: reducing cardiovascular events.

✓ Kidney effects: increase of renoprotection.

✓ There are no interactions with immunosuppressants mediated by CYP (cytochrome P450 enzymes)

Table 1. Published studies with GLP-1 RA use in KT

Study id	Study design, follow-up	Population	Intervention/s	Outcome
Pinelli *et al.* [17]	• Case series, $n = 5$ • Follow-up: 3 weeks	KT recipients with or without previous DM or PTDM, with stable renal function receiving tacrolimus	All patients received liraglutide in monotherapy	• Reduction of postprandial blood glucose levels at 60 (7.3 ± 1.2 versus 5.9 ± 0.5 mmol/L) and 120 min (7.1 ± 0.8 versus 6.0 ± 0.4 mmol/L); no decrease of FBS • Reduction in body weight after 3 weeks (−2.1 ± 1.3 kg)
Halden *et al.* [18]	• RCT, $n = 24$ (PTDM $n = 12$, without PTDM $n = 12$)	KT with and without PTDM	Intravenous infusion of GLP-1 versus saline (placebo)	• GLP-1 improves glucose-induced insulin secretion and glucagon suppression in PTDM patients
Liou *et al.* [19]	• Retrospective case series, $n = 7$ • Mean follow-up: 19.4 ± 7.6 months	KT recipients with PTDM treated with liraglutide	All patients received liraglutide	• Decrease of FBS from 228.6 ± 39.1 to 166.0 ± 26.6 mg/dL ($P = 0.103$) • Reduction of HbA1c from 10.0 ± 1.6% to 8.1 ± 0.8% ($P = 0.017$) • Weight loss from 78.0 ± 7.8 to 77.7 ± 12.3 kg ($P = 0.922$)
Singh *et al.* [20]	• Retrospective case series, $n = 63$ • Follow-up: 24 months	SOT recipients with DM using dulaglutide *Includes both type-2 DM (43 patients) and PTDM (20 patients)	All patients received dulaglutide	• Statistically significant weight reduction: mean paired difference at 6, 12 and 24 months of 2.07 ($P < 0.003$), 4.007 ($P < 0.001$) and 5.23 ($P < 0.034$) kg • Insulin reduction: mean paired difference of 5.94 units ($P < 0.0002$)
Singh *et al.* [21]	• Retrospective cohort, $n = 88$ (dulaglutide $n = 63$, liraglutide $n = 25$) • Follow-up: 24 months	SOT patients with DM treated with dulaglutide or liraglutide *Includes both type-2 DM (43 patients) and PTDM (20 patients)	All patients received dulaglutide or liraglutide	• Significant weight decrease with dulaglutide compared with liraglutide (2% versus 0.09%; $P = 0.003$) • Reduction in insulin units with dulaglutide compared with liraglutide (26% versus 3.6%; $P = 0.01$) • No statistical differences between groups in HbA1c changes

FBS, fasting blood sugar; SOT, solid organ transplant.

Dipeptidyl Peptidase-4 inhibitors (DPP-4i)

- In the case of PTDM, DPP-4i have these potential roles:

✓ Metabolic impact:

Repairing pathophysiological aetiologies of insulin resistance and b-cell dysfunction.

Use as adjunctive therapy: lowering insulin requirements early post-transplantation.

Reducing obesity

✓ Cardiovascular effects: No studies in KTx.

✓ Kidney effects: Reduce Albuminuria

Table 2. Published studies with DPP-4i use in KT

Study id	Study design, follow-up	Population	Intervention/s	Outcome
Lane *et al.* [36]	• Case series, $n = 15$ • Follow-up: 3 months	KT recipients with eGFR >30 mL/min/1.73 m^2 and diagnosis of PTDM	All patients treated with sitagliptin	• Reduction in HbA1c from 7.2 ± 0.1% to 6.7 ± 0.2% (P = 0.002) • No patient discontinuation because of side effects • No symptomatic hypoglycaemia
Sanyal *et al.* [37]	• Case series, $n = 21$ • Follow-up: 6 months	KT recipients with diagnosis of PTDM and stable renal function *Immunosuppression: prednisone 5 mg/day and standard dose of tacrolimus	All patients received linagliptin monotherapy (5 mg/day)	• Decrease in FPG of 22.21 mg/dL and decrease in postprandial plasma glucose of 40.07 mg/dL (P < 0.01) • Decrease of HbA1c 0.6% in 24 weeks
Soliman *et al.* [38]	• RCT, $n = 62$ • Follow-up: 3 months	KT recipients with PTDM receiving metformin and inadequate glycaemic control	Metformin + sitagliptin versus metformin + insulin * Rescue therapy: pioglitazone	• Similar reduction in HbA1c in both groups (−0.6 ± 0.5% with sitagliptin and −0.6 ± 0.6% in insulin group) • Small weight loss in sitagliptin group (−0.4 kg) and weight gain in insulin group (+0.8 kg); P < 0.05 • No severe adverse events
Boerner *et al.* [39]	• Case series, $n = 22$ • Mean follow-up: 32.5 ± 17.8 months	KT recipients with diagnosis of PTDM treated with sitagliptin alone	All patients treated with sitagliptin monotherapy	• Mean HbA1c 6.5 ± 0.5%. • No episodes of pancreatitis • Rare transplant-specific adverse events
Haidinger *et al.* [40]	• Phase II RCT, $n = 33$ • Follow-up: 4 months	KT recipients (>6 months post-KT) with stable renal function and diagnosis of PTDM	Vildagliptin 50 mg/day versus placebo during 3 months	• Reduced HbA1c (6.1% versus 6.5%, P < 0.05) and 2HPG (182.7 versus 231.2 mg/dL, P < 0.05) in the vildagliptin group versus placebo • Mild adverse events, similar rates in both groups
Strøm Halden *et al.* [41]	• RCT cross-over, $n = 19$ • Follow-up: 8 weeks	KT recipients (>1a) with PTDM and stable renal function	4 weeks with sitagliptin followed by 4 weeks with no sitagliptin, versus vice versa * Also includes patients with other oral antidiabetic treatment, maintained with same dose	• Significant increase of insulin secretion with sitagliptin • Decrease in FPG [0.9 (0.5–1.7) mmol/L; P = 0.003] and 2HPG [2.9 (0.5–6.4) mmol/L; P = 0.004]
Guardado-Mendoza *et al.* [42]	• Prospective cohort study, $n = 28$ • Follow-up: 12 months	KT recipients with fasting hyperglicaemia during the first 24 h post-surgery	Linagliptin 5 mg/days plus insulin versus insulin alone	• Lower glucose levels (131.0 ± 15.1 versus 191.1 ± 22.5 mg/dL) and insulin doses (37.5 ± 6.3 versus 24.2 ± 6.6 U) in the linagliptin + insulin group (P < 0.05) • Less severe hypoglicaemia in linagliptin + insulin group (65.1 ± 2.2 versus 54.2 ± 3.3 mg/dL; P = 0.036)

FPG, fasting plasma glucose.

Sodium Glucose Co-transporter 2 Inhibitors (SGLT2i)

- The benefits of SGLT2i use on kidney function have been widely reported in type 2 DM.
- Five RCTs in type 2 DM patients and in non diabetics (EMPA-REG ,CANVAS , DECLARE, CREDENCE and DAPA-CKD) have concluded that treatment with SGLT2i is capable of slowing the progression of CKD.
- In case of PTDM, SGLT2i have these potential roles:

✓ Metabolic impact: reducing HbA1c and reducing obesity

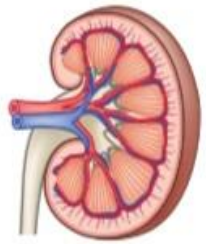
✓ Cardiovascular effects: improving cardiovascular outcomes after KT.

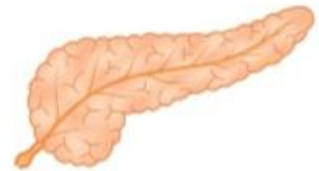
✓ Kidney effects: improving renal function and outcomes of the graft.

Table 3. Published studies with SGLT2i use in KT

Study id	Study design, follow-up	Population	Intervention/s	Outcome
Rajasekeran *et al.* [59]	• Case series, $n = 11$ • Follow-up: 80.5 person-months after canaglifozin initiation	KT ($n = 6$) and SPKT ($n = 4$) recipients treated with canaglifozin	All patients treated with canaglifozin	• No urinary nor mycotic infections. No major complications • Small reductions in eGFR (-4.3 ± 12.2 mL/min/1.73 m^2; $P = 0.3$), but no episodes of AKI • Discrete HbA1c reduction of $-0.84 \pm 1.2\%$ ($P = 0.07$)
Schwaiger *et al.* [60]	• Prospective interventional study, $n = 14$ • Follow-up: 4 weeks ($n = 14$), 12 months ($n = 8$)	KT with PTDM receiving treatment with insulin and eGFR >30 mL/min/1.73 m^2	Four weeks on stable insulin treatment, and after a 3-day insulin wash-out, conversion to empaglifozin in monotherapy. Reinstitution of insulin if poor glycaemic control *Concomitant antidiabetic drugs were discontinued	• Increased FPG from 111 ± 21 to 144 ± 45 mg/dL ($P = 0.005$) and 2HGP from 232 ± 82 to 273 ± 116 mg/dL ($P = 0.06$) in 4 weeks • Decrease of body weight from 83.7 ± 7.6 to 81.6 ± 7.4 kg in 4 weeks ($P = 0.03$) and to 78.7 kg in 12 months ($P = 0.02$) • Decrease of eGFR from 55.6 ± 20.3 to 47.5 ± 15.1 mL/min/1.73 m^2 ($P = 0.008$). Not statistically significant differences in 12 months
Attallah *et al.* [61]	• Case series, $n = 8$ • Mean follow-up: 12 months	KT treated with empaglifozin (previous DM $n = 4$, PTDM $n = 4$)	All patients treated with empaglifozin *Some patients taking concomitant antidiabetic drugs	• Slight initial worsening of renal function, but then stabilized (mean SCr from 88.5 to 99.5 mmol/L) • Mean decrease of HbA1c of 0.85% • Mean decrease of body weight of 2.4 kg • Two patients developed UTI
Halden *et al.* [62]	• RCT, $n = 49$ • Follow-up: 24 weeks	KT recipients with diagnosis of PTDM	Empaglifozin ($n = 22$) versus placebo ($n = 22$)	• Statistically significant reduction of HbA1c compared with placebo: median -0.2% (IQR -0.6, -0.1) versus 0.1 (-0.1, 0.4); $P = 0.025$ • Median reduction of body weight of -2.5 kg (IQR -4.0, -0.05) compared with placebo group ($P = 0.014$) • No significant differences in adverse events or eGFR
Mahling *et al.* [63]	• Case series, $n = 10$ • Median follow-up: 12 months	KT recipients receiving empaglifozin and eGFR >45 mL/min/1.73 m^2 *Includes PTDM and previous DM diagnosis	All patients received empaglifozin	• eGFR remained stable • Slight decrease in the median of HbA1c of 0.2% ($P > 0.05$) • Median decrease of body weight -1.0 kg (IQR -1.9, -0.2 kg)

FPG, fasting plasma glucose; IQR, interquartile range; SPKT, simultaneous pancreas-kidney transplant.



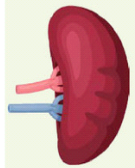
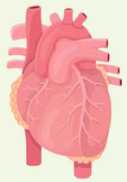
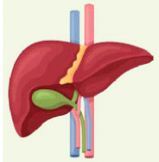
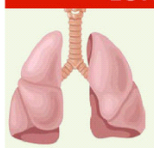


	Renal benefits	Cardiovascular benefits	Metabolic impact
GLP-1 RA	? ↓ eGFR decline ? ↓ Albuminuria	? ↓ Cardiovascular events	↑ Insulin secretion and ↓ glucagon secretion, with better glycemic control Weight loss
DPP4i	? ↓ Albuminuria		↓ Insulin resistance and β-cell dysfunction: ↓ insulin requirements and better glycemic control Weight loss
SGLT2i	? ↓ Hyperfiltration ? ↓ Albuminuria	? ↓ Systolic blood pressure	Weight loss

FIGURE 2: Summary of renal, cardiovascular and metabolic actions of GLP-1 RA, DPP-4i and SLGLT2i.

Management of post-transplant diabetes: immunosuppression, early prevention, and novel antidiabetics

POTENTIAL BENEFITS OF SGLT2 INHIBITORS AND GLP1-RAs IN SOLID ORGAN TRANSPLANT PATIENTS

		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)

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Conclusions

- PTDM is a common and important complication after solid organ transplantation.
- The development of PTDM is associated with an increased risk of graft failure, premature CVD and CV death.
- Identifying patients at risk of PTDM particularly in the waiting list, is crucial to prevent the disease and its complications.
- Management of PTDM remains the most controversial issue since the 2013 consensus recommendations.
- Novel antidiabetics are promising drugs to prevent complications and slow progression of kidney disease.

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