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DIABETIC Medicine

REVIEW ARTICLE

Association of British Clinical Diabetologists and Renal Association guidelines on the detection and management of diabetes post solid organ transplantation

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Abstract

Post-transplant diabetes mellitus (PTDM) is common after solid organ transplantation (SOT) and associated with increased morbidity and mortality for allograft recipients. Despite the significant burden of disease, there is a paucity of literature with regards to detection, prevention and management. Evidence from the general population with diabetes may not be translatable to the unique context of SOT. In light of emerging clinical evidence and novel anti-diabetic agents, there is an urgent need for updated guidance and recommendations in this high-risk cohort. The Association of British Clinical Diabetologists (ABCD) and Renal Association (RA) Diabetic Kidney Disease Clinical Speciality Group has undertaken a systematic review and critical appraisal

of the available evidence. Areas of focus are; (1) epidemiology, (2) pathogenesis, (3) detection, (4) management, (5) modification of immunosuppression, (6) prevention, and (7) PTDM in the non-renal setting. Evidence-graded recommendations are provided for the detection, management and prevention of PTDM, with suggested areas for future research and potential audit standards. The guidelines are endorsed by Diabetes UK, the British Transplantation Society and the Royal College of Physicians of London. The full guidelines are available freely online for the diabetes, renal and transplantation community using the link below. The aim of this review article is to introduce an abridged version of this new clinical guideline (https://abcd.care/sites/abcd.care/files/site_uploads/Resources/Position-Papers/ABCD-RA%20PTDM%20v14.pdf).

1 | INTRODUCTION

Solid organ transplantation (SOT) for people with end organ failure is a well-established and life-saving treatment. Whilst diabetes mellitus (DM) is recognised as the most important cause of kidney failure worldwide and a common cause for renal transplantation,[1] development of post-transplant hyperglycaemia in non-diabetic people is a common consequence of renal and other SOT. Post-transplant diabetes mellitus (PTDM), previously termed new onset diabetes after transplantation (NODAT), is common in people undergoing SOT, and associated with adverse clinical outcomes.

Due to generic and transplant-specific risk factors, PTDM should be considered as a distinct pathophysiological entity. The aim of this guideline is to focus specifically on dysglycaemia or DM recognised primarily *after* transplantation. We recognise, however, many such people may have undetected pre-transplant DM. Indeed, the term NODAT was changed to PTDM by a Consensus report in 2014, to reflect time of diagnosis rather than time of onset.[2] We focus on renal transplantation but include some data on other SOT where available. While these recommendations focus on PTDM, they are relevant for SOT recipients with pre-existing diabetes who are likely to suffer glycaemic deterioration post-transplantation. The management of DM following the failing/failure of the pancreas in simultaneous pancreas-kidney transplants is not addressed in these guidelines.

Evidence grades for the recommendations

The following evidence grading has been used to determine the strength of the recommendations; the suggested audit standards; and the questions for areas that require future research.

1A—Strong recommendation: high-quality evidence
1B—Strong recommendation: moderate-quality evidence
1C—Strong recommendation: low-quality evidence
1D—Strong recommendation: very low-quality evidence
2A—Weak recommendation: high-quality evidence
2B—Weak recommendation: moderate-quality evidence
2C—Weak recommendation: low-quality evidence
2D—Weak recommendation: very low-quality evidence

Search strategy

The recommendations are based on a systematic review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase, using the following key words: new onset diabetes after transplantation, post-transplant diabetes, renal transplant and diabetes, liver transplant and diabetes, cardiac transplant and diabetes, lung transplant and diabetes.

2 | EPIDEMIOLOGY OF PTDM

2.1 | Incidence and prevalence of PTDM

Box 1 outlines some recommendations for epidemiology of PTDM. Prior to a 2003 Consensus report,[3] reported incidence and prevalence of PTDM varied significantly and reflected heterogenous clinical practice. Different immunosuppressive regimens, mixed diagnostic criteria and diverse transplant cohort demographics meant reported incidence and prevalence rates were not comparable.[4] The 2003 consensus meeting formulated guidelines on diagnosis, prevention and management of PTDM.[3] Reported incidence of PTDM varies between 9% and 39% in the first year, and likely reflects

distinct patient demographics and immunosuppression practice.[5] Beyond the first year, it is difficult to determine whether the incremental risk of developing PTDM is over and above the incremental risk of developing diabetes in the general population. With increasing longevity of both transplant recipients and their allograft, the presumption is that the cumulative exposure to diabetogenic risk factors (both traditional and transplant-specific) leads to continued risk for PTDM.[6]

Some studies suggest that the incidence of PTDM is declining, possibly due to rationalised immunosuppression or reduced rejection. Contemporary immunosuppression regimens adopt calcineurin inhibitor (CNI) sparing regimens (to avoid the risk of nephrotoxicity), and this reduced exposure may reduce the risk of PTDM. In a Norwegian single-centre analysis, the odds of developing PTDM appear to have halved between 1997 and 2007.[7]

2.2 | Impact of PTDM on long-term patient/graft outcomes

Some studies suggest that PTDM is associated with increased risk of mortality after transplantation,[8-10] although this is not consistently reported.[11] The lack of robust data collection by national transplant registries for PTDM is a major factor limiting the accurate assessment of the impact of PTDM on mortality.

The association between PTDM and graft loss is unclear. While an association with overall graft loss is well recognised (driven by mortality), the association between PTDM and death-censored graft loss is uncertain.[10-15]

2.3 | Impact of PTDM on morbidity

Rejection remains the leading cause of patient concern, but the relationship between PTDM and rejection may not be bi-directional. Treatment for allograft rejection includes corticosteroid boluses, which increases risk for PTDM, but it is unclear if PTDM leads to an increased risk for rejection, (although pre-existing diabetes appears to increase this risk).[16]

A number of studies have shown an association between PTDM and increased risk of cardiovascular disease (CVD).[17,18] While this risk may not be as high as in those with pre-existing diabetes, it likely reflects the difference in cumulative exposure to glycaemia, or the presence of metabolic syndrome. In addition, pre-diabetes has been suggested as a risk factor for the development of CVD in people with PTDM.[19]

Data on PTDM and risk of microvascular complications are limited. One study observed the emergence of diabetes-related microvascular complications within three years in over half of kidney transplant recipients who developed PTDM.[20] Here, the median time to onset of microvascular complications was 1.8 years, contrasting sharply with non-transplant diabetes. This contrasts with more recent data from 64 people with PTDM of at least 5-year duration, who had a lower than expected prevalence of microvascular complications compared to the general population living with diabetes, with little evidence of retinopathy, but higher prevalence of neuropathy.[21] In people with diabetes undergoing

BOX 1 Recommendations, future research and suggested audit standards: Epidemiology

RECOMMENDATIONS

1. Data relating to diagnosis of post-transplant diabetes mellitus (PTDM) using specific diagnostic criteria should be routinely collected for accurate auditing of incidence, prevalence and outcomes in all transplant centres (Ungraded).
2. Micro- and macrovascular outcome data for solid organ transplant recipients with PTDM should be collected (Ungraded)

AREAS FOR FUTURE RESEARCH

1. Determine the incidence of PTDM longitudinally post-transplantation among different patient cohort groups (e.g. age, gender, body mass index, ethnicity).
2. How does the standardised incidence ratio differ for development of diabetes comparing a transplant versus general population cohort?
3. What are the long-term outcomes associated with PTDM across different population cohorts?
4. Does progression of micro- and macrovascular complications differ for patients with PTDM compared to other forms of diabetes mellitus (DM)?
5. Do micro- and macrovascular outcomes differ for patients with PTDM compared to other forms of DM?
6. Is the epidemiology of PTDM changing in the contemporary climate of solid organ transplantation?

AUDIT RECOMMENDATIONS

1. What proportion of PTDM patients are recorded correctly in hospital and primary care records?
2. What proportion of patients with PTDM have regular screening for microvascular complications of diabetes?

renal transplantation, diabetic nephropathy can recur.[22] In people with PTDM, development of de novo diabetic nephropathy seen on renal biopsy has been reported in eight out of 81 people with diabetes.[23]

3 | PATHOGENESIS OF PTDM

Box 2 outlines recommendations for pathogenesis of PTDM. PTDM may be considered a distinct metabolic entity from other forms of diabetes and its pathogenesis reflects this separation. Risk factors for PTDM can be categorised as non-modifiable versus modifiable, or generic versus transplant-specific (Table 1). Knowledge of PTDM risk factors is evolving. For example, data are conflicting with regards to whether adult polycystic kidney disease is a risk factor for PTDM, with published studies showing positive or negative associations.[24,25] Understanding PTDM risk factors is important to help risk stratify and counsel transplant recipients, facilitate additional support or consider pre-emptive modification to attenuate PTDM risk.

BOX 2 Recommendations, future research and suggested audit standards: Pathogenesis

RECOMMENDATIONS

1. Counselling of risk for post-transplant diabetes mellitus (PTDM) should consider individualised risk factors (Grade 1B)

AREAS FOR FUTURE RESEARCH

1. Clarify risk factors for development of PTDM in context of uncertain or conflicting published literature (e.g. risk for PTDM with polycystic kidney disease)
2. Does the pathophysiology of early onset PTDM differ from late-onset PTDM?
3. What contribution do individual risk factors make as part of the combined risk for PTDM?
4. Is a stratified approach to high-risk patients for diagnosis, prevention and/or management effective to prevent PTDM?
5. How can the pre-transplant genetic risk for PTDM be utilised in a clinical application to reduce risk?

AUDIT RECOMMENDATIONS

1. What proportion of patients are informed of their risk for developing PTDM whilst awaiting transplantation?

TABLE 1 Current understanding of risk factors for PTDM

Non-modifiable	Modifiable
• Age • Ethnicity • Black • Hispanic • South-Asian • Family history of diabetes mellitus • Cause of end-stage renal failure • Polycystic kidney disease • Gender • HLA mismatch • Deceased-donor kidney • Genetics • Innate immunity	• Previous stress related hyperglycaemia • Obesity • Metabolic syndrome • Pre-transplant triglycerides • Cytomegalovirus • Hepatitis C • Immunosuppression • Tacrolimus • Ciclosporin • Sirolimus • Corticosteroids • Basiliximab • Rejection episodes • Anti-hypertensive medications • Beta blockers • Thiazide diuretics • Reduced glomerular filtration rate • Hypomagnesaemia

Post-transplant diabetes mellitus develops in the context of declining insulin secretion, in the presence of insulin resistance and is supported by mechanistic research.[7] However, both general and transplant-specific risk factors influence pathophysiology. For example, calcineurin inhibitors (CNIs) are strongly linked to PTDM,[26] and associated with decreased insulin sensitivity in context of diminished insulin secretion.[27] Tacrolimus trough level reduction is shown to improve β-cell secretion, suggesting the diabetogenic risk of CNIs is dose-dependent. CNIs up-regulate insulin gene expression and decrease insulin synthesis by transcriptional inhibition of insulin mRNA,[28] and may affect insulin secretion through reversible toxicity to the β-cell.[29] This effect appears to be strongest in people with high triglycerides (seen in patients with metabolic syndrome) [30] and may be due to an interaction between tacrolimus and free fatty acids in the β-cell leading to β-cell dysfunction.[31]

The role of glucocorticoids in the development of PTDM relates to their interference with carbohydrate metabolism and insulin secretion/action via a number of mechanisms, including inducing insulin resistance by down-regulating insulin receptors in liver, muscle and adipose tissue. Recent work from genome-wide association studies supports the hypothesis that β-cell dysfunction is critical in the development of PTDM, with a number of single-nucleotide polymorphisms identified in genes that are associated with β-cell apoptosis.[32]

The current consensus is that β-cell dysfunction is the dominant pathophysiological defect in early PTDM, with insulin resistance being the major contributor later in the condition.

4 | DETECTION OF PTDM

Box 3 outlines the recommendations for detection of PTDM. Consensus guidelines for PTDM have aligned themselves with ADA recommendations,[2] and emphasise the clinical relevance of pre-diabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]). Pre-diabetes is a risk factor for development of PTDM, and IGT per se may be an independent predictor of mortality.[33]

Although early postoperative hyperglycaemia, common after renal transplantation, may be a risk factor for subsequent development of PTDM, it should not be used as a diagnostic criterion since many cases are transient. Diagnosis should be made in a stable clinical period, at least 6 weeks after transplantation.[2]

BOX 3 Recommendations, future research and suggested audit standards: Detection of post-transplant diabetes mellitus (PTDM)

RECOMMENDATIONS

1. Avoid diagnosis of PTDM in the first 6 weeks post operatively when transient hyperglycaemia is extremely common (Grade 1B).
2. Afternoon capillary blood glucose monitoring (AGM) is recommended to identify patients with postoperative hyperglycaemia. These patients need close monitoring and formal testing for PTDM when clinically stable (Grade 1B).
3. A formal diagnosis of PTDM can be made from 6 weeks post-transplantation using an oral glucose tolerance test (Grade 1B).
4. Oral glucose tolerance test is the current gold standard for diagnosis of PTDM. While it may not be practical to use routinely in all solid organ transplant recipients prospectively, it should be utilised when possible for additional risk stratification and/or diagnostic clarification (Grade 1B).
5. $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) combined with fasting plasma glucose (FPG) ≥7.0 mmol/l are suitable diagnostic tests in clinically stable solid organ transplant recipients after the first 3 months post-transplantation. In asymptomatic patients, the abnormal test should be repeated after 2 weeks to confirm the diagnosis (grade 1B).
6. Caution with the use of HbA_{1c} must be exercised in the presence of factors that may impair accurate interpretation (Grade 1A).
7. In stable patients combining the results from abnormal FPG ≥7 mmol/L and/or HbA_{1c} ≥6.5% (48 mmol/mol) will detect the majority of PTDM cases (Grade 2C).
8. Patients awaiting transplant should receive annual glycaemic testing with FPG +/− HbA_{1c}. High-risk patients should then go on to have oral glucose tolerance test (OGTT) to confirm diagnosis of diabetes or screen for impaired glucose tolerance (IGT, Grade 2C).
9. The use of novel diagnostic tools such as fructosamine and glycated albumin are undetermined and cannot be recommended as clinical tools (Grade 2D)

AREAS FOR FUTURE RESEARCH

1. Does method of PTDM detection impact upon long-term outcomes?
2. Do solid organ transplant recipients with transient hyperglycaemia post-transplant have an increased risk for future PTDM?
3. What are the long-term outcomes for solid organ transplant recipients with impaired fasting glucose (IFG), IGT or pre-diabetes?
4. Does risk of PTDM differ for recipients with IFG versus IGT?
5. Are there any additional benefits from fructosamine and/or glycated albumin as diagnostic tools for PTDM?

AUDIT RECOMMENDATIONS

1. Is there a formal protocol for screening for pre-existing diabetes in people awaiting transplantation?
2. What proportion of patients are screened for hyperglycaemia in the immediate post-transplant period?
3. What proportion of patients following transplantation undergo yearly HbA_{1c} screening?

4.1 | Fasting plasma glucose

Fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL) is a criterion for the diagnosis of DM, although it requires more than one abnormal value in the absence of symptoms [60]. IFG is defined by the ADA as FPG 5.6–6.9 mmol/L, and the World Health Organisation as 6.1–6.9 mmol/L.

Fasting plasma glucose is a relatively easy screening method for glucose homeostasis alterations but has several limitations. Isolated elevation of FPG is a consequence of hepatic insulin resistance with normal muscle insulin sensitivity, often combined with defects in early-phase insulin secretory response.[34] In non-transplanted subjects, IFG is more common in men than in women, with minimal overlap with IGT. In stable kidney transplant recipients without a known history of diabetes, the prevalence of isolated IFG has been reported to be 12%–18%, isolated IGT in 9% and combined IFG/IGT in 12%–14%.[35] In both general and transplant populations, sole determination of FPG would miss a third of people with PTDM who have an isolated defect in glucose tolerance.[35] Normal FPG in people with IGT may occur in renal disease due to reduced renal clearance of insulin.

Some transplant centres have reported hybrid approaches, combining diagnostic tools (e.g. OGTT) stratified by threshold FPG level.[36] During the first 4–6 weeks after transplantation, FPG alone is of low value to detect hyperglycaemia, but despite these limitations, people with high FPG values have poorer outcomes in graft and patient survival.[37]

4.2 | 2-h plasma glucose during OGTT

Oral glucose tolerance test is widely accepted as the gold standard for diagnosis of PTDM and remains the diagnostic test of choice in most PTDM guidelines (FPG ≥ 7.0 mmol/L or 2 h glucose ≥ 11.1 mmol/L).[2] Disadvantages include poor reproducibility and logistical obstacles for routine use, suggesting it should be reserved for use in specific situations where diagnostic clarification of PTDM is essential.

4.3 | Glycated haemoglobin

Since the adoption of HbA_{1c} as a diagnostic tool for DM in 2009,[38] the utility of HbA_{1c} in the diagnosis of PTDM has been debated. Falsely high HbA_{1c} levels can be observed with acidosis [39] and iron deficiency,[40] while falsely low HbA_{1c} levels can result from blood loss, blood transfusions, shortened erythrocyte survival time and erythropoietin.[40] During the first year after kidney transplantation, anaemia may be present in 50%.

Prospective long-term data using HbA_{1c} as a diagnostic tool for PTDM with analysis of macro- and microvascular complications are lacking, but several smaller studies have explored the utility of HbA_{1c} post kidney transplantation. Some have shown better sensitivity than FPG,[41] good concordance with OGTT results[42] and 83% sensitivity for detection of PTDM with cut-off ≥5.8% (40 mmol/mol) to avoid need for OGTTs.[36] HbA_{1c} is of poor diagnostic value in the first 3 months due to anaemia, but predicts risk of pre-diabetes and PTDM at 1 and 3 years after kidney transplantation.[43] Some studies suggest that HbA_{1c} may detect PTDM only in a minority of cases detected by OGTT.[44] Early use of HbA_{1c} was shown to be highly specific but poorly sensitive to diagnose PTDM in a recent meta-analysis.[45] HbA_{1c} measurement may therefore be considered in stable kidney transplant recipients for the detection of transplant associated hyperglycaemia and PTDM beyond 3 months after transplantation, ideally in combination with FPG. Whilst certain caveats in comparison to OGTT exist, its ease of use makes it an attractive diagnostic tool.

4.4 | Continuous glucose monitoring

Continuous glucose monitoring (CGM) devices offer the ability to obtain glucose profiles over days and weeks and aid understanding of post-transplant hyperglycaemia. CGM monitoring has shown that people with T2D demonstrate higher glycaemic variability (GV) than people with PTDM[46] and detects hyperglycaemic episodes that would have remained undetected by routine laboratory testing.[47,48] CGM may therefore be useful in the detection of early postoperative hyperglycaemia as FPG may be normal, HbA_{1c} unreliable and OGTT impractical.

4.5 | Fructosamine and glycated albumin

Fructosamine and glycated albumin are alternative measures for glycaemia but their link to average glucose and their prognostic significance are less clear. Fructosamine correlates with glycaemic control during the previous 1–3 weeks. Determination of fructosamine as an index of diabetic control has not shown any benefit in the care of diabetes people over blood glucose and HbA_{1c} monitoring,[49] and is thus, usually used in situations where HbA_{1c} is unreliable. The paucity of data related to fructosamine or glycated albumin means their standard use cannot be recommended currently.

5 | MANAGEMENT OF PTDM

Box 4 outlines the recommenations for management of PTDM. Distinct categories of hyperglycaemia may be seen following organ transplantation, including pre-existing diabetes

BOX 4 Recommendations, future research and suggested audit standards: Management

RECOMMENDATIONS

1. Immediately post-transplant, early postoperative hyperglycaemia (glucose >11.0 mmol/L on two occasions within 24 h) should be actively monitored and treated. If hyperglycaemia is mild (<14.0 mmol/L), then oral hyperglycaemic therapy can be considered. Otherwise, early insulin therapy should be instituted either intravenously or subcutaneously (Grade 1C).
2. Glycaemic target for people with post-transplant diabetes mellitus (PTDM) should be around 7% (53 mmol/mol), but adjusted according to degree of chronic kidney disease, age, co-morbidity, ability to self-manage and patient preference (Grade 1B).
3. All people with a confirmed diagnosis of PTDM should be offered structured diabetes education (Grade 1B).
4. The diagnosis of PTDM must be conveyed to the patients' usual primary care practitioner, and the patient should be put on to a diabetes register (ideally coded as 'PTDM'), and offered structured diabetes care, along with regular screening for complications (Grade 1B).
5. If patients with a stable eGFR ≥ 30 mls/min/1.73 m^2 and BMI ≥ 25 kg/m^2, metformin (dose adjusted for eGFR) should be considered first line oral therapy for people with confirmed PTDM (Grade 1C).
6. Other therapies which may be used safely in PTDM include sulfonylureas, meglitinides, dipeptidylpeptidase-4 inhibitors, pioglitazone and glucagon-like peptide-1 analogues. Use of sulfonylureas and meglitinides should be undertaken with care especially in those at risk of hypoglycaemia, and doses should be adjusted according to eGFR (Grade 2C)
7. Sodium glucose transporter-2 (SGLT-2) inhibitors should be used with caution in patients with stable eGFR ≥ 30 mls/min/1.73 m^2 and poor glycaemic control in patients at low risk of urinary tract infection, after careful discussion with nephrology and diabetes specialists (Grade 1C).
8. Insulin therapy should be considered in all patients who have inadequate glucose control, or who have symptomatic hyperglycaemia (Grade 1C).
9. Blood pressure should be controlled below 130/80 mmHg in all people with PTDM (Grade 1B).
10. All people with PTDM should be offered statin therapy, irrespective of cholesterol level (Grade 2D).
11. All people with PTDM should have access to specialist diabetes expertise within a multidisciplinary team setting (Grade 1C).

AREAS FOR FUTURE RESEARCH

1. What is the optimum management for in-patient hyperglycaemia in patients undergoing renal transplantation?
2. Is there a benefit of tight versus standard glucose control in the early or late post-transplant period?
3. Are low carbohydrate diets effective for management of PTDM?
4. What is the role of SGLT-2 inhibitors and glucagon-like peptide-1 analogues in the management of PTDM?
5. Does choice of immunosuppressive regimen influence onset and management of PTDM?

AUDIT RECOMMENDATIONS

1. What proportion of patients with PTDM have good glycaemic control as determined by their individualised glycaemic target?
2. What proportion of patients with PTDM and stable eGFR above 30 mls/min/1.73 m^2 are treated with metformin?
3. What proportion of patients with a diagnosis of PTDM are offered structured diabetes education, and have regular foot and eye screening?

(sometimes previously undetected), transient hyperglycaemia in the early postoperative period and persistent PTDM.[50] Treatment of dysglycaemia post-transplantation can be divided into treatment of acute hyperglycaemia in the early postoperative period, and longer-term treatment once renal function and immunosuppression is more stable (usually at around 3 months post-transplant). A suggested pathway for glycaemic management of PTDM is shown in Figure 1.

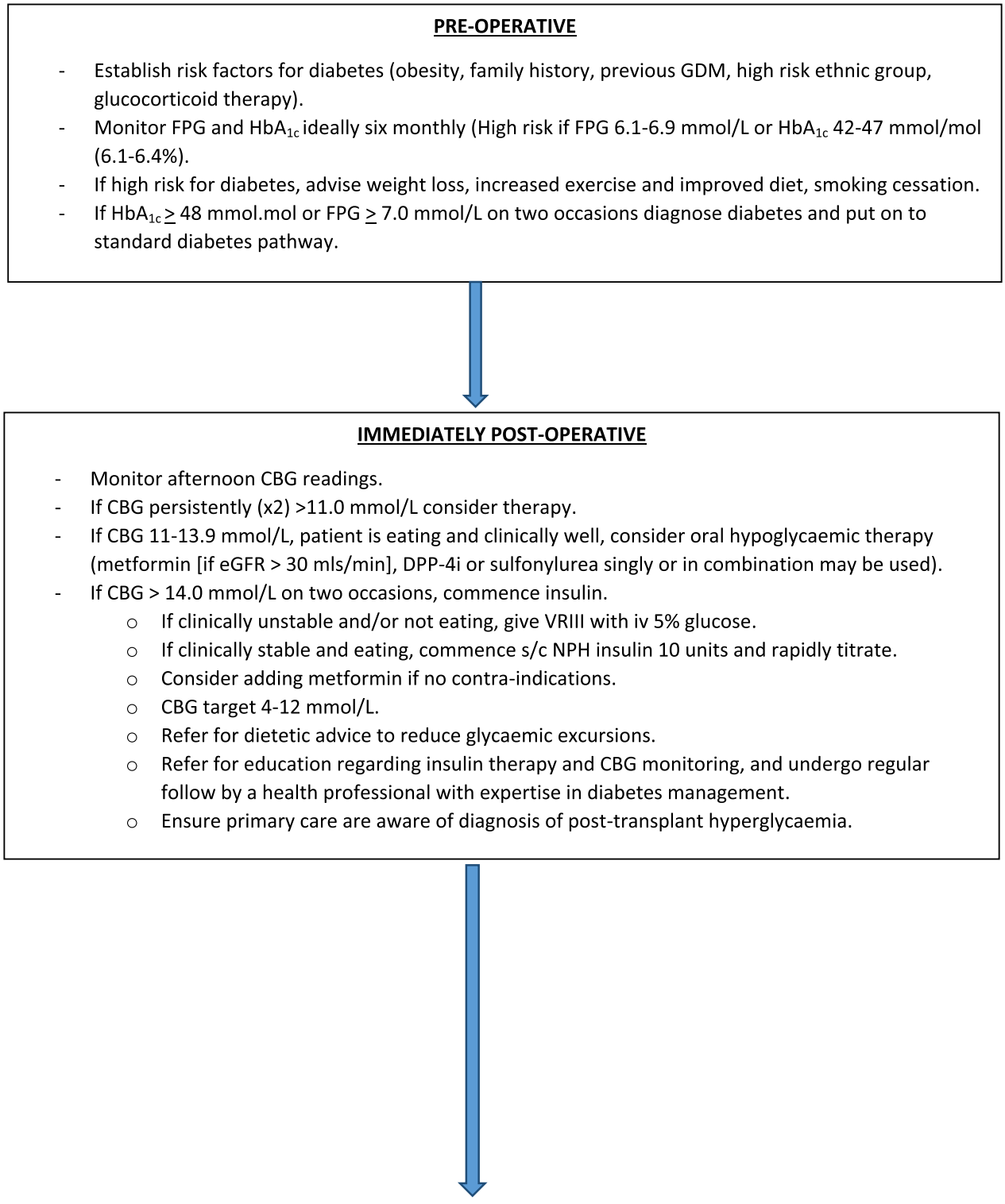

FIGURE 1 Pathway for diagnosis and management of PTDM

5.1 | Early postoperative hyperglycaemia and glucose management in hospital

Dysglycaemia in the early postoperative period following transplantation is secondary to a constellation of aetiological factors. It is frequent and has been associated with poor outcomes including risk for long-term PTDM, rejection, infection, delayed graft function, graft loss and death [S1].

Corticosteroids are important during induction of immunosuppression, and early post-transplant hyperglycaemia shares some similarities with steroid-induced diabetes. The Joint British Societies Guidelines on the Management of

UPTO SIX WEEKS POST OPERATIVE

- Regular review with aim to reduce glucocorticoid dose, stabilise immunosuppression, *consider* conversion to less diabetogenic CNI therapy (eg ciclosporin) if no signs of rejection and stable graft function.
- Reduce oral hypoglycaemic therapy or insulin if possible.
- Ensure diet and lifestyle changes are optimised.
- At six weeks, consider OGTT if practical.
- During OGTT, if FPG ≥7.0 mmol/L or 2 hour PG ≥11.1 mmol/L diagnosis PTDM and treat as below.

THREE MONTHS POST OPERATIVE

If CBG well controlled and HbA1c at target, consider reduction in anti-hyperglycaemic therapy with careful self-monitoring of CBG.

If hyperglycaemia resolved (CBG < 11 mmol/L) off anti-hyperglycaemic therapy, screen for PTDM with OGTT if possible, but if not, request HbA_{1c} and FPG.

- If HbA_{1c} ≥ 48 mmol.mol or FPG ≥ 7.0 mmol/L on two occasions diagnose PTDM
  - Ensure patient and their primary health care team are informed of the diagnosis and the diagnosis is coded on the patients electronic care record.
  - Refer patient for structured education and regular screening of eyes, feet, kidneys, blood pressure, weight, smoking status and lipids.
  - Manage cardiovascular risk factors.
  - Individualise glycaemic target according to patients preference and co-morbidities.
  - Drugs such as metformin (if eGFR > 30 ml/min/1.73m^2), gliptins, GLP-1 analogues, and insulin can all be used safely post transplantation.
  - Avoid pioglitazone and saxagliptin in heart failure.
  - Seek specialist advice when considering SGLT2 inhibitors.

- If HbA_{1c} < 42 mmol.mol (6.0%) and FPG < 6.0 mmol/mol, PTDM is not diagnosed and hyperglycaemia has resolved.
  - Continue to monitor HbA_{1c} and FPG at 12 months and then annually.

- If HbA_{1c} 42-47 mmol.mol (6.0-6.4%) or FPG 6.1-6.9 mmol/L, patient is at risk of developing PTDM
  - Continue to monitor HbA_{1c} and FPG at 6 monthly intervals.
  - Offer lifestyle advice to reduce risk of developing PTDM.

FPG – fasting plasma glucose; HbA_{1c} – glycated haemoglobin; CBG – capillary blood glucose; DPP-4i – dipeptidylpeptidase-4 inhibitor; VRIII – variable rate intravenous infusion of insulin; NPH – Neutral protamine Hagedorn; CNI – calcineurin inhibitor; 2 hour PG – 2 hour plasma glucose; eGFR- estimated glomerular filtration rate; PTDM – post transplant diabetes mellitus; SGLT2 – sodium glucose transporter-2

FIGURE 1 (Continued)

TABLE 2 Glycaemic targets in people with diabetes and Diabetic Nephropathy-CKD

	Glycaemic target	Note
Type 1 diabetes	48–58 mmol/mol (6.5%–7.5%)	Younger patients within 10 years' duration of diabetes and variable microalbuminuria–CKD stage 2
	58–62 mmol/mol (7.5%–7.8%)	The majority of patients with proteinuria and/or CKD stages 3–4
	58–68 mmol/mol (7.5%–8.5%)	Patients with CKD stage 5-dialysis
Type 2 diabetes	48–58 mmol/mol (6.5%–7.5%)	For the majority of patients who are aged <40 years, or have CKD stages 1–2 (no basis to aim for <52 mmol/mol (6.9%) unless the patient is aged <40 years and has CKD stages 1–2)
	52–58 mmol/mol (6.9%–7.5%)	For those with CKD stages 3–4 this target may be appropriate with a GLP−1–SGLT−2 inhibitor-based treatment regimen without insulin
	58–68 mmol/mol (7.5%–8.5%)	For those with CKD stages 3–4-proteinuria who are on an insulin-based regimen, and those with CKD stage 5 who are on dialysis

Hyperglycaemia and Steroid Therapy offer consensus-based guidelines on glucose management with corticosteroids [S2]. Post-transplant hyperglycaemic emergencies do occur, and exclusion of diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome is important. Significant hyperglycaemia (glucose ≥ 14.0 mmol/L) should be managed actively with subcutaneous insulin (if patient is eating and drinking) or variable rate intravenous insulin infusion, intravenous fluids and hourly blood glucose monitoring. Lower levels may be managed with oral hypoglycaemic agents. In similar to in-patient settings such as myocardial infarction or intensive care, there is no evidence to support very tight glucose control, and there is even some suggestion of harm [S3]. Once the patient is stabilised, conversion from intravenous to subcutaneous insulin should be undertaken, usually to a once-daily isophane insulin (preferably given in the morning), with additional prandial insulin as needed.

5.2 | Glycaemic targets in PTDM

Active monitoring of glucose control is important after transplantation. Some observational studies suggest poorer graft outcomes with poorer control. A Korean study of 3538 kidney transplant recipients suggested that the highest quartile of time-averaged glucose was related to poor graft outcomes (graft failure or death) [S4]. A further cohort study of 798 renal transplant recipients showed that being in the highest quartile of maximal glucose increased the adjusted risk of death by a factor of 2.2 [S5]. In the absence of clinical evidence showing improved PTDM outcomes with better glucose control, however, targets used in T2D are probably appropriate for people with PTDM. The American Diabetes Association (ADA) suggests an overall glucose target of 7.0% (53 mmol/mol), but less stringent targets may be appropriate [S6]. KDIGO recommends a glycaemic target of 7%–7.5% (53–58 mmol/mol) after renal transplantation [S7]. The Association of British Clinical Diabetologists-RA guidelines on managing hyperglycaemia in people with diabetes and diabetic nephropathy-chronic kidney disease suggest less stringent targets according to grade of CKD; we believe should apply to PTDM [S8] (Table 2).

5.3 | Glucose-lowering therapies in PTDM

As the therapeutic armamentarium for management of hyperglycaemia increases, a number of newer therapies are available to manage glucose in PTDM. Many have not been adequately tested in PTDM and a personalised approach is warranted. Risk of interaction with immunosuppressants should be considered. For example ciclosporin inhibits cytochrome P450 3A4 enzyme, and may increase levels of prandial glucose regulators, dipeptidylpeptidase-4 inhibitors (DPP-4i), sulfonylureas and possibly sodium glucose transporter-2 (SGLT-2) inhibitors, although this is rarely clinically important [S9].

5.3.1 | Diet and lifestyle-based management

Weight gain is common following transplantation, and dietetic input for transplant patients is important [S10]. In one study of 33 people randomised to intensive versus standard dietary intervention, weight gain was limited to 5.5 kg in the

intensive group, compared to 11.8 kg in the standard group [S11]. Higher weight pre-transplantation is a risk factor for PTDM and should be a target for prevention.

A clinical trial of dietitian delivered active versus passive lifestyle intervention in 130 renal transplant recipients showed no change in glycaemic indices of metabolism but did demonstrate reduction in fat mass and weight, and possibly a reduced incidence of PTDM, which did not reach significance (7.6% vs. 15.6%, $p = 0.123$) [S12]. A prospective study of 468 renal transplant recipients showed that a Mediterranean diet was associated with lower PTDM risk [S13].

5.4 | Oral hypoglycaemics

5.4.1 | Metformin

In the post-transplant setting, metformin should be considered for management of PTDM if renal function allows, with appropriate dose adjustment (reduced to 500 mg twice daily in eGFR ≤45 mls/min/1.73 m^2 and stopped if eGFR falls ≤30 mls/min/1.73 m^2). In a large US survey of 14,144 renal transplant recipients, 4.7% received metformin within 12 months post-transplant, and they had significantly lower all-cause, malignancy-related and infection-related mortality [S14]. In a further observational study of 46,914 transplant recipients, <10% received metformin, but they had better transplant survival and lower mortality [S15]. Selection bias for people with better renal function being prescribed metformin may have contributed to these findings.

Metformin is first-line therapy for treatment of T2D in many guidelines and has been suggested as a potential first-line agent for treatment of PTDM [S16]. In transplant patients with stable renal function and no other contraindications, metformin should be encouraged.

5.4.2 | Sulfonylureas/Meglitinides

Due to their rapid efficacy and ease of administration, sulfonylureas are commonly used in people with PTDM with limited clinical efficacy data [S17]. Repaglinide has been shown to lower HbA_{1c} in a small observational study [S18]. Whilst useful in the early post-transplant period, both classes must be balanced with the risk of hypoglycaemia, particularly when immunosuppressive regimes are being titrated.

5.4.3 | Thiazolidinediones

Thiazolidinediones have been shown to be safe and effective in small studies of people with PTDM. In one study of 10 patients treated with insulin or glyburide post-transplant, the addition of pioglitazone lowered HbA_{1c} by 1.4% (12 mmol/mol) and reduced the dose of insulin [S19]. A study of non-diabetic renal transplant recipients randomised to pioglitazone or placebo showed a modest benefit in carotid intima-media thickening [S20]. In a further study of 40 people with PTDM initially stabilised with insulin, adding rosiglitazone at 3 months post-transplant led to only 3/40 subsequently requiring insulin [S21]. They may be useful to treat liver steatosis post liver transplant [S22]. Fluid retention, weight gain and increased fracture risk limit their use.

5.4.4 | DPP-4 inhibitors

Dipeptidylpeptidase-4 inhibitor drugs are useful in people with PTDM as they have few side effects, although they have modest efficacy. A number studies have reported the use of DPP-4i in PTDM, but have all been small scale, short duration and not randomised. A meta-analysis of five DPP-4i studies in PTDM suggested an approximate 1% (11 mmol/mol) reduction in HbA_{1c}, with no effect on eGFR [S23].

5.4.5 | Glucagon-like peptide-1 analogues

Glucagon-like peptide-1 (GLP-1) analogues are increasingly used in CKD. In the largest reported cohort in SOT ($n = 63$), patients treated with dulaglutide showed a mean weight reduction at two years of 5.23 kg, insulin dose reduction of 5.94 units, although no significant improvement in glycaemic control was seen [S24].

5.4.6 | SGLT-2 inhibitors

Sodium glucose transporter-2 inhibitors are accruing significant clinical evidence for cardio- and reno-protection in the non-transplant setting [S25]. In PTDM, potential side effects (genito-urinary infection or euglycaemic ketoacidosis) are a concern. In a placebo-controlled study ($n = 44$), a modest reduction in HbA_{1c} of 0.2% (2 mmol/mol) was seen with reduced weight and no difference in adverse events [S26]. No cardiorenal protection data are available in PTDM.

5.4.7 | Insulin

There is no randomised study of insulin regimens in PTDM. As early postoperative hyperglycaemia may be managed with once-daily neutral protamine hagedorn insulin, this seems the regimen of choice for most people, particularly as

it may usefully reduce postprandial hyperglycaemia which is typical of steroid-induced hyperglycaemia. As steroid doses are weaned, insulin doses must be carefully titrated. Longer term, insulin therapy may be required in PTDM, and standard regimens such as basal insulin, twice-daily fixed mixtures or basal bolus regimens may be used.

Management of cardiovascular risk factors in people with PTDM

Cardiovascular disease remains a significant problem after SOT [S27]. As PTDM increases this risk, cardiovascular risk reduction is important, although traditional cardiovascular risk factors may not be highly predictive of cardiac events [S28]. Smoking cessation, however is mandatory, as there is a high risk of allograft failure in smokers compared to non-smokers, and smoking may increase the risk of PTDM [S29].

Dyslipidaemia is common amongst people undergoing transplantation. The Assessment of LEscol in Renal Transplantation study randomised over 2100 low-risk renal transplant recipients to fluvastatin or placebo, and despite a 32% reduction in LDL cholesterol, no significant difference in major adverse cardiovascular events (MACE) was seen [S30]. A Cochrane meta-analysis of 17 studies of statin use in renal transplant recipients showed non-significant reductions in MACE (RR 0.84, 95% CI 0.66–1.06), cardiovascular death (RR 0.68, 95% CI 0.45–1.01) and myocardial infarction (MI – RR 0.70, 95% CI 0.48–1.01) [S31]. Nevertheless, KDIGO guidelines suggest statin therapy for all renal transplant recipients [S7], aiming for a target LDL cholesterol below 100 mg/dl (2.6 mmol/L).

Hypertension is common post-transplantation and, if uncontrolled, associated with adverse graft outcomes. Unlike CKD settings, renin-angiotensin aldosterone system blockers lack evidence for improved outcomes. There is some suggestion that calcium channel blockade may be beneficial in hypertension post-transplantation [S32]. There is currently no strong evidence for the optimum BP target for renal transplant recipients. KDIGO guidelines suggest a target BP of 130/80 mmHg [S7], which concords with the target of 130/80 mmHg in people with diabetic kidney disease [S33].

Structured diabetes care and screening for diabetes complications

There may be a lower rate of microvascular complications in PTDM versus people with T2D, but in those who develop complications, progression may be accelerated, justifying regular surveillance. All people with PTDM should therefore be registered in a primary care diabetes register, and receive standard screening and management within primary care. Close liaison with the transplant team, however, will be required when additional therapy for glucose or cardiovascular risk factors is warranted. In large transplant centres, PTDM may be effectively managed in a multidisciplinary clinic involving diabetes and renal specialists.

6 | MODIFICATION OF IMMUNOSUPPRESSION TO PREVENT OR TREAT PTDM

Box 5 outlines recommendations in modification of immunosuppression in the management of PTDM. Immunosuppressive therapy used in SOT includes induction therapy (antithymocyte globulin, basiliximab and alemtuzumab) and maintenance therapy (corticosteroids, CNIs, azathioprine, mycophenolate mofetil, mTOR inhibitors (sirolimus and everolimus) and belatacept.

Contemporary guidance advocates choosing immunosuppression to prolong patient/graft survival rather than prevention of PTDM [S34]. Immunosuppression should be personalised to each patient for stratified risk/benefit and it is notable that protocols in the UK are heterogenous between transplant units. The diabetogenic potential for various immunosuppressive drugs is shown is Table 3.

6.1 | Corticosteroids

There is debate on risk/benefit of corticosteroid-sparing regimens post-transplantation. Some RCTs show no effect of steroid-sparing regimens on PTDM incidence, whilst others have shown reduced PTDM. Steroid-sparing regimens may involve either rapid reduction of steroid dose, or complete cessation within a short timescale. Meta-analysis of 34 studies ($n = 5637$), steroid-sparing regimens after kidney transplantation was associated with lower risk for PTDM, higher risk for rejection, worse graft function and equivalent patient/graft survival [S35]. By contrast, however, some studies have shown no increase in acute or chronic rejection rates with steroid-free regimens. One such study ($n = 25{,}837$) was associated with reduced odds of developing PTDM within three years [S36]. With 15-year follow up, retrospective analysis of 1553 kidney transplant patients suggested that rapid discontinuation of steroids was associated with reduced onset of PTDM without any impact on graft function or patient/graft survival [S37]. Two recent RCTs, Harmony ($n = 615$) and ADVANCE ($n = 1081$) both showed reduced PTDM with steroid-sparing regimens with no increase in rejection [S38, S39].

These discrepant findings may be explained by the diabetogenic effects of CNIs reducing any potential benefits of steroid-sparing regimens. It is also possible high CNI trough levels are responsible for the absence of beneficial effects of steroid-sparing on incidence of PTDM. In view of continued uncertainty, further research in this area is warranted.

BOX 5 Recommendations, future research and suggested audit standards: Modification of immunosuppression

RECOMMENDATIONS

1. Whilst immunosuppression is a major risk factor for post-transplant diabetes mellitus (PTDM), any planned modification to attenuate this risk should be balanced against the risk for allograft rejection (Grade 1B).
2. Individualisation of immunosuppression based on the recipient's immunologic and glycaemic risk must be taken as part of an overall strategy to improve long-term transplant outcome (Grade 1C).
3. Until further evidence emerges, we adopt the recommendation that the choice of immunosuppressive therapy should be primarily to prevent rejection rather than preventing PTDM (Grade 1C).
4. There is no evidence to suggest changing immunosuppressive therapy when hyperglycaemia is detected has a role in the management of PTDM (Grade 2B).
5. There is as yet no evidence that newer agents such as belatacept are beneficial in reducing risk of PTDM compared to tacrolimus-based regimens (Grade 1C).

AREAS FOR FUTURE RESEARCH

1. PTDM should be included as a clinical endpoint in randomised controlled trials of new immunosuppressive agents.
2. How do the competing risks of PTDM and rejection compare as risk factors for adverse long-term clinical outcomes?
3. Is there any glycaemic benefit from prolonged-release versus immediate-release tacrolimus formulations?
4. In low immunological risk patients at high risk for PTDM, does a modified immunosuppression regimen (e.g. steroids sparing, CNI conversion) lead to improved short-term (e.g. PTDM, rejection) and long-term (graft function, cardiovascular events, graft loss, mortality) clinical outcomes?
5. Explore the risks and benefits of newer immunosuppressive agents as they enter clinical practice (e.g. PTDM vs. other complications).

AUDIT RECOMMENDATIONS

1. How many transplant units have stratified immunosuppression regimens for renal transplant candidates at increased risk for PTDM?

TABLE 3 Commonly used immunosuppressive drugs and their diabetogenic risk

	Post-transplant diabetes mellitus risk
Corticosteroids	Increased
Tacrolimus	Increased
Ciclosporin	Slightly increased
mTORi	Slightly increased
Mycophenolate mofetil	No effect
Azathioprine	No effect
Belatacept	Slightly decreased?
Basiliximab	Slightly increased?

6.2 | Calcineurin inhibitors

CNIs increase risk for PTDM, with tacrolimus showing greater diabetogenic risk than ciclosporin.[26] In an open-label, multicentre RCT, tacrolimus-based immunosuppression with steroid maintenance was found to provide the best balance between PTDM and acute rejection (compared to ciclosporin or steroid avoidance) [S40]. The authors suggested tacrolimus-to-ciclosporin conversion in people with inadequately controlled PTDM after the early-phase post-transplantation may be considered.

A more recent tacrolimus-to-ciclosporin conversion RCT ($n = 80$) found 39% of people in the ciclosporin arm were off glucose-lowering medication versus 13% in the tacrolimus arm at 12 months ($p = 0.01$) [S41]. Risk for rejection was not increased, but ciclosporin conversion was associated with reduced renal function. Economic evaluation suggested that ciclosporin offered the second-best net health benefit after immediate release-tacrolimus for people at risk of complications from diabetes, and some advocates support this strategy [S42].

Calcineurin inhibitor-sparing is a further strategy to reduce risk of PTDM, but meta-analyses give conflicting results [S43, S44].

6.3 | mTOR inhibitors

A meta-analysis including 33 trials ($n = 7114$ renal transplant recipients) observed no differences in incidence of PTDM with mTORi [S45]. Large registry analysis showed that sirolimus increases risk of PTDM, with the most diabetogenic combination being concomitant CNI use [S46]. A recent meta-analysis exploring conversion from CNI to everolimus included 11 RCTs ($n = 1633$), and observed lower incidence of PTDM (4.92% vs. 8.29%, $p = 0.16$), but increased risk for rejection at 1 year (risk ratio 1.82 [1.11–2.99]) [S47].

An RCT including 613 renal transplant recipients showed that everolimus plus low-dose tacrolimus facilitates reduced CNI exposure, while achieving good renal function, low graft loss, with similar incidence of hyperglycaemia at 12 months (24.8% vs. 27.0%) [S48].

6.4 | Other agents

Belatacept blocks CTLA-4, leading to selective blockade of T-cell activation. It has been shown in RCT to reduce incidence of PTDM compared to ciclosporin [S49]. In a meta-analysis of RCTs ($n = 1535$), belatacept-based immunosuppression had equivalent patient/graft survival but less kidney scarring and reduced risk for PTDM [S50]. When compared to tacrolimus-based regimens, belatacept has less risk for PTDM. Cost and logistical issues with parenteral administration have limited wider use of belatacept.

Observational data have suggested that basiliximab (a monoclonal antibody to CD25) is associated with PTDM, while meta-analyses do not identify any association [S51].

6.4.1 | PREVENTION OF PTDM

6.5 | Lifestyle intervention

Box 6 outlines recommendations for prevention of PTDM. Prevention or delay of T2D is feasible by means of lifestyle intervention or pharmacotherapy [S52]. More recently, remission of T2D has been achieved in people treated with very low-calorie diets [S53]. PTDM has additional risk factors that may be modifiable (e.g. immunosuppression). Lifestyle intervention for prevention of PTDM has been discussed in Section 4.

Bariatric surgery has a potent effect on prevention (or remission) of T2D in high-risk people. In haemodialysis patients, there may be a role for bariatric surgery to prevent development of PTDM. In one series of 24 haemodialysis patients undergoing bariatric surgery, pre-operative BMI mean was 41 kg/m^2, and dropped to a mean of 28 kg/m^2, facilitating transplantation in 16 people [S54].

BOX 6 Recommendations, future research and suggested audit standards: Prevention

RECOMMENDATIONS

1. The risk for development of diabetes should be assessed as part of a pre-transplant work-up for all people being considered for transplantation (Grade 1B).
2. All people awaiting transplantation should be educated on the risk of developing post-transplant diabetes mellitus (PTDM), should be counselled about minimising weight gain using lifestyle measures and should see a dietitian with expertise in this area (Grade 1B).
3. Treatment of risk factors for PTDM such as hepatitis C should be considered in patients awaiting transplantation (Grade 1C).
4. In people considered at high risk for the development of PTDM, consideration should be given to immunosuppressive therapy that is less prone to inducing hyperglycaemia but this should be based on individualised risk with immunological status in mind (Grade 1C).
5. All patients deemed at high risk for development of PTDM should be screened yearly for diabetes whilst awaiting transplantation (Grade 1B).

AREAS FOR FUTURE RESEARCH

1. What is the role of standard risk scores for predicting the development of PTDM?
2. Does intensive lifestyle intervention prevent the development of PTDM?
3. Is there a role for pharmacotherapy (metformin, GLP-1 analogues, orlistat) in the prevention of PTDM?

AUDIT RECOMMENDATIONS

1. What proportion of patients awaiting transplantation are risk assessed for the development of PTDM?

6.6 | Pharmacological intervention

In the non-transplant setting, a number of pharmacological agents have been shown to prevent or delay the onset of T2D high-risk individuals. Amongst renal transplant recipients,

a study of 48 people with stable renal transplants and IGT treated with 3 months of vildagliptin or pioglitazone led to a significant reduction in 2-h glucose, although no wash out period was used in this study, so prevention of PTDM was not established [S55]. Studies are planned using metformin and DPP-4i to prevent PTDM.

In a pilot RCT, intensive and early basal insulin therapy versus standard care lowered PTDM risk at 12-months by 73%, possibly due to β-cell protection from stress hyperglycaemia [S56]. Larger studies are in progress to evaluate this further. Treatment of hepatitis C, a significant PTDM risk factor, with α-interferon prior to renal transplantation has shown reduced risk for PTDM [S57]. Choice of immunosuppressive regimen may also reduce risk of PTDM in high-risk individuals as has been discussed earlier.

7 | PTDM CONSIDERATIONS IN THE NON-RENAL SETTING

Box 7 outlines recommendations concerning PTDM in the non-renal setting. Whilst most PTDM literature is in the setting of kidney transplantation, the burden of PTDM translates across other forms of SOT [S58]. General considerations are translatable across different solid organ settings. There are, however, some unique aspects to take into consideration with each specific organ.

7.1 | PTDM after liver transplantation

7.1.1 | Epidemiology and outcomes

Registry data suggest rates of PTDM after liver transplantation up to 40% [S59]. Non-alcoholic steatohepatitis (NASH) is a common cause of end-stage liver disease and transplant registry data confirm that liver transplant recipients with NASH are more likely to develop PTDM. Hepatitis C, a common cause of end-stage liver disease, also increases risk for PTDM [S60]. A combination of these aetiological factors perhaps explains why incidence of PTDM is highest after liver transplantation. Registry data regarding outcomes are conflicting, although emerging data suggest increased mortality, and CVD associated with PTDM after liver transplantation [S59]. Weight gain is common following liver transplantation and should be mitigated. Treatment of hepatitis C virus may reduce risk of PTDM [S57].

7.1.2 | Liver transplant caveats for diagnosis and management

PTDM diagnostic classification should remain the same for liver transplant recipients, but there are specific considerations. Many liver transplant recipients will have renal impairment so the same precautions with HbA_{1c} still apply. In addition, interpretation of HbA_{1c} in the context of advanced liver disease may be difficult due to anaemia. Management of diabetes in the setting of liver impairment can be challenging as the liver is the major site of metabolism for many anti-diabetic medications, but metformin may be considered if liver allograft function and renal function is good.

BOX 7 Recommendations, future research and suggested audit standards: PTDM in the non-renal setting

RECOMMENDATIONS

1. Organ-specific factors should be considered when counselling patients for their risk of PTDM prior to solid organ transplantation (Grade 1B)
2. The diagnosis of PTDM should be consistent across different solid organ transplant settings, with organ-specific caveats in mind to determine the optimal diagnostic test (e.g. accuracy of HbA_{1c}; Grade 1C)
3. The management of PTDM should be consistent across different solid organ transplant settings, with organ-specific caveats in mind to determine the optimal management strategy (Grade 1B)

AREAS FOR FUTURE RESEARCH

1. What are the long-term outcomes for solid organ transplant recipients who develop PTDM?
2. Is the evolution on abnormal glucose metabolism post-transplantation different among different solid organ transplant settings?
3. Should solid organ transplant recipients receive the same management intervention strategy?

AUDIT RECOMMENDATIONS

1. What proportion of non-renal solid organ transplant patients are risk assessed for the development of PTDM prior to transplantation?
2. What proportion of non-renal solid organ transplant patients are screened for post-transplant hyperglycaemia and PTDM?
3. What proportion of patients undergoing non-renal solid organ transplants have good glycaemic control as determined by their individualised glycaemic target?

7.2 | PTDM after heart transplantation

7.2.1 | Epidemiology and outcomes

Registry data report PTDM rates of 25%–28% and 20% 5 years after heart transplantation [S61], with shared risk factor development as other SOTs, but outcome data are limited. For example, diabetes is a known risk factor for death within a year of heart transplantation (hazard ratio 1.37, 95% CI 1.15–1.62) but does not distinguish between pre-transplant and PTDM [S62].

7.2.2 | Heart transplant caveats for diagnosis and management

Whilst there are no specific diagnostic considerations, PTDM management must consider sub-optimal heart allograft function. Thiazolidinediones and saxagliptin have a propensity to develop heart failure and should be avoided. The propensity for renal impairment and hyperkalaemia increases in the setting of heart failure and should lead to individualised pharmacological therapy for heart transplant recipients if there is sub-optimal heart allograft function.

7.3 | PTDM after lung transplantation

7.3.1 | Epidemiology and outcomes

A significant proportion of lung transplant recipients develop PTDM. In a prospective single-centre study using OGTT in 156 lung transplant recipients (25 with pre-existing diabetes), rates of PTDM after 3, 12 and 24 months were 32%, 30% and 24% respectively in surviving patients [S63]. Registry data show PTDM incidence rates of approximately 30% and 40% among surviving lung transplant recipients by 5 years [S64]. The incidence of PTDM appears greater in people with cystic fibrosis, with half of patients having diabetes prior to lung transplantation and half of the remaining developing PTDM post-transplant [S65]. Outcome data remain limited for lung transplant recipients who develop PTDM. A single-centre study from Melbourne analysing 210 lung transplant recipients demonstrated an increased risk of mortality with increasing degrees of hyperglycaemia but did not distinguish people with pre-transplant versus PTDM [S66].

7.3.2 | Lung transplant caveats for diagnosis and management

No specific caveats exist in the diagnosis or management of PTDM in the setting of lung transplantation above and beyond those already discussed in other sections.

8 | CONCLUSIONS

Observational studies involving hard outcomes of graft loss or mortality suggest that the diagnosis of PTDM is an important contributor to morbidity and mortality following SOT. The condition deserves careful monitoring and management, ideally by a multidisciplinary team of specialists with combined expertise. This guideline has reviewed the current knowledge base and made evidence-based recommendations for the transplantation community.

The majority of studies in this area have been short-term, under-powered and used surrogate outcomes, and as a result large areas of uncertainty exist, and further research is warranted to develop evidence-based care for SOT recipients with, or at risk of, diabetes.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

Tahseen Chowdhury, Mona Wahba, Ritwika Mallik, Javeria Peracha and Adnan Sharif undertook the literature searches and first draft of the guidance. All other authors reviewed, re-reviewed and contributed to further revisions of the guidelines. TAC and AS are guarantors.

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