

Post-transplantation diabetes: clinical challenges

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Abstract

Post-transplantation diabetes mellitus (PTDM) is a common complication seen after kidney transplantation and is associated with adverse outcomes. There is a lack of robust evidence-based medicine to guide clinical decision making in the prevention or management of PTDM. Despite the availability of professional society guidelines and expert consensus reports, this paucity of data translates into clinical challenges in day-to-day practice for transplant and diabetes professionals. In this article, four common clinical scenarios associated with PTDM are discussed which offer advice for bridging the gap between evidence-based guidelines and real-world practice.

Key words: post-transplantation diabetes; kidney transplantation, renal transplantation, immunosuppression, obesity

Introduction

Post-transplantation diabetes mellitus (PTDM) is a common complication associated with kidney transplantation which significantly contributes to morbidity and mortality. To help transplant and diabetes professionals, the Association of British Clinical Diabetologists and the UK Kidney Association (ABCD-UKKA) have produced joint professional society guidelines on the detection and management of PTDM.¹ These are complemented by an expert consensus document from the Third International PTDM Consensus Meeting,² which provides statements on areas where there is an absence of a clear underlying evidence base, prohibiting firm recommendations.

This is important as, while research has enhanced our understanding over the last few decades, distinct gaps remain in the published literature that challenge our decision-making for optimal clinical management of PTDM. In this article, after a brief overview outlining the importance of improving our prevention and management of PTDM, four common

scenarios typically faced by practising clinicians are outlined and discussed.

The burden of PTDM

The incidence of PTDM after kidney transplantation is high: it is observed in approximately 20% of kidney allograft recipients within the first year after surgery.³ It shares features of both type 1 and 2 diabetes (T1DM and T2DM), but remains a distinct pathophysiological entity. PTDM is associated with adverse clinical outcomes, including increased risk for overall graft loss, cardiovascular disease and all-cause mortality.³ Microvascular complications have been studied less and other long-term consequences of PTDM require further evaluation. PTDM is important as any kidney transplant patient is at risk, due to a combination of generic and transplant-specific risk factors. Many pre-transplant risk factors are common to T2DM (such as obesity, metabolic syndrome), but immunosuppression is the most important post-transplant risk factor. Development of diabetes is a leading worry for kidney transplant patients themselves.⁴ An oral glucose tolerance test (OGTT) is strongly encouraged as the gold-standard tool for screening and diagnosis of PTDM. While its logistical challenges are appreciated, an OGTT has better diagnostic sensitivity, stronger association with adverse outcomes and identifies both components of pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance). Importantly, OGTTs allow earlier identification of at-risk individuals on the waiting list,⁵ which is important for risk counselling but also implementation of risk mitigation strategies. Therefore, centres should try to incorporate the use of OGTTs into their clinical practice for kidney transplant candidates and recipients.

Clinical challenge 1: Can I prevent PTDM in my high cardio-metabolic risk kidney transplant candidate?

While there are many modifiable post-

transplant risk factors for PTDM, perhaps the most important is immunosuppression. Despite the association between immunosuppression and PTDM, current advice is to avoid routinely modifying de novo regimens to mitigate PTDM risk or adjusting after PTDM development. However, for some kidney transplant candidates or recipients, tailored immunosuppression to prevent or manage PTDM may be justified if the negative consequences of diabetes are deemed to outweigh other competing risks (such as rejection) on a case-by-case basis.

In a systematic review and meta-analysis of the published literature, Oliveras *et al.* analysed the association between immunosuppressive drug combinations commonly used after kidney transplantation and risk for PTDM.⁶ In total, the analysis included 125 randomised controlled trials (RCTs), of which 124 were available for empirical analysis. No association was seen between induction therapies and PTDM risk. An increased PTDM risk was observed with tacrolimus versus ciclosporin (relative risk [RR] 1.71, 95% CI [1.38-2.11]). Tacrolimus in combination with a mammalian target of rapamycin inhibitor (mTORi) versus mycophenolic acid had the same PTDM risk. There was a tendency towards a higher risk of PTDM in the ciclosporin with mTORi group versus mycophenolic acid (RR 1.42, 95% CI [0.99-2.04]), while conversion from ciclosporin to an mTORi increased PTDM risk (RR 1.89, 95% CI [1.18-3.03]) versus remaining on ciclosporin. While tacrolimus is considered more diabetogenic than ciclosporin, the combination of the latter with mTORi may have a higher PTDM risk although heterogenous ciclosporin trough levels in the included studies may be a confounder. The co-stimulatory blocker belatacept resulted in 50% lower risk of PTDM (RR 0.50, 95% CI [0.32-0.79]) versus tacrolimus or ciclosporin. Steroid avoidance resulted in 31% lower PTDM risk (RR 0.69, 95% CI [0.57-0.83]) versus

steroid maintenance, but steroid withdrawal had no difference on PTDM risk versus steroid maintenance.

While these associations with PTDM are important for consideration, they must be balanced against competing post-transplant risks including rejection, infections and cancers. Therefore, recommendations state that clinicians must choose immunosuppressant regimens that provide the best overall survival for kidney transplant patients and be mindful of all competing risks.

Beyond immunosuppression, other interventions could possibly mitigate PTDM risk. Post-transplant hypomagnesaemia is common and has been associated with PTDM risk. However, despite encouraging data in the general population,⁷ RCTs post-transplantation show no benefit of magnesium supplementation on glycaemia.⁸ Prevention of cytomegalovirus viraemia or disease after transplantation, the commonest opportunistic infection, is important to avoid adverse outcomes but could reduce PTDM risk due to a positive association between the two.⁹

Perhaps the most important modifiable risk factor would be targeting obesity and prevention of weight gain. There is convincing evidence that bariatric surgery is beneficial for individuals with morbid obesity and chronic kidney disease (CKD). A non-randomised study reported no cases of PTDM in 12 kidney transplant recipients without diabetes after post-laparoscopic sleeve gastrectomy, in comparison to three of 18 patients from a matched non-laparoscopic sleeve gastrectomy control group (statistically not significant).¹⁰ Glucagon-like peptide-1 receptor agonists might be a promising pharmacological option for individuals with advanced CKD and obesity who are transplant candidates but require weight loss. While this has the potential to prevent PTDM risk after surgery, RCT evidence is currently lacking.

Clinical challenge 2: How do I manage a new kidney transplant patient who develops post-op PTDM?

For post-operative hyperglycaemia, early

exogenous insulin administration should be considered for immediate clinical management and for potential long-term PTDM prevention. While a recent multi-centre RCT did not show any significant difference in the primary endpoint (1-year PTDM incidence) with such an approach in the intention-to-treat analysis, a significant difference in PTDM rates was observed in the per-protocol analysis.¹¹ This discrepancy arose from the higher hypoglycaemia rates observed, and appropriate safety netting will be necessary for close management in an outpatient setting.

As highlighted above, immunosuppression changes in the immediate post-operative setting should only be considered in exceptional circumstances as mitigation of glycaemic risk must be counter-balanced with competing risks. Regardless of pharmacological interventions, non-pharmacological intervention is extremely important. While transplant-specific guidance on lifestyle intervention lacks a strong evidence base, lifestyle modification should be emphasised post-transplantation based upon evidence from the general population.¹²

Clinical challenge 3: Can I use SGLT-2 inhibitors for my kidney transplant patient with PTDM?

Novel agents like sodium-glucose co-transporter 2 (SGLT-2) inhibitors dominate diabetes treatment guidelines.¹³ Cardiovascular outcome trials using glucose-lowering treatment after transplantation are lacking but retrospective analyses suggest that major adverse cardiovascular events and mortality are lowered after kidney transplantation with SGLT-2 inhibitor use. Sheu and colleagues assessed the efficacy of SGLT-2 inhibitors in kidney transplant recipients with diabetes at the time of transplantation using the TriNetX network (an international electronic health record data network). In a propensity score-matched analysis, with a median follow-up of 3.4 years, SGLT-2i users showed significantly lower rates of all-cause mortality (adjusted hazard ratio [aHR]: 0.32), major adverse cardiac events (aHR: 0.48), and major adverse kidney

events (aHR: 0.52).¹⁴ Studies specifically in patients with PTDM are smaller but also suggestive of cardiovascular benefit.¹⁵

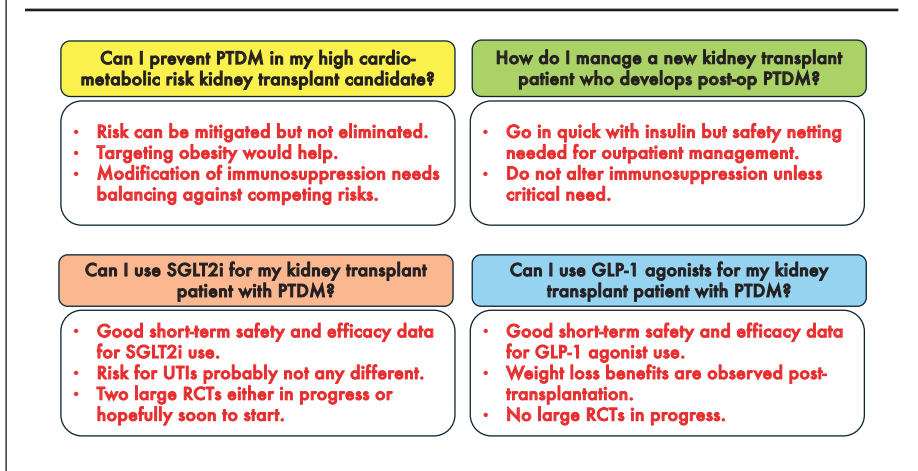
Reassuringly, some prospective RCTs are in progress. For example, the Renal Lifecycle Trial (<https://renal-lifecycle.com/en/home-en/>) is currently recruiting 1,500 patients with advanced chronic kidney disease or kidney failure (including ~500 kidney transplant patients) to explore the effects of dapagliflozin on renal and cardiovascular outcomes. While these results are eagerly awaited, there are many reasons to believe that kidney transplant patients have more chance of benefit than harm from SGLT-2 inhibitors. Novel agents are likely to be under-utilised for PTDM management due to limitations of transplant-specific evidence. However, uptake is sub-optimal even in kidney disease patients with diabetes who meet national/international recommendations,¹⁶ which reflects a disconnect between clinical guidelines and real-world practice.

SGLT2 inhibitors have shown short-term safety and efficacy in the setting of kidney transplantation. While there is no restriction on early use post-operatively, many clinicians prefer to wait until kidney allograft function is stable and/or ureteric stents have been removed to reduce the risk for infection. However, it is important to note that urinary tract infection risk does not appear to be any higher for kidney transplant recipients with versus without exposure to SGLT-2 inhibitors.¹⁷ The risk for euglycaemic diabetic ketoacidosis must be acknowledged, especially in patients with insulin deficiency. Although SGLT-2 inhibitors should be suspended if fasting is required or during an acute illness, it is important to recommence them at the earliest opportunity.

Clinical challenge 4: Can I use GLP-1 agonists for my kidney transplant patient with PTDM?

Like SGLT-2 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists are novel agents that dominate diabetes treatment guidelines.¹³ Several non-randomised published reports indicate acceptable short-term safety and efficacy data for kidney transplant recipients, with

Figure 1. Summary of four common clinical challenges relating to kidney transplant candidates at risk of PTDM before surgery or kidney transplant recipients who develop PTDM after surgery



no increased rejection or graft failure risk, although gastrointestinal side effects are common. They are an attractive choice for obese kidney transplant recipients with or at risk for PTDM. In a systematic review and meta-analysis of nine published studies (n=338), GLP-1 agonists were shown to be effective in reducing proteinuria and improving glycaemic control and weight loss in kidney transplant recipients, without altering tacrolimus levels, but increased gastrointestinal symptoms were observed.¹⁸ No robust cardio-renal outcomes were available for analysis. At present, no large prospective RCT is exploring robust cardio-renal outcomes with GLP-1 agonist use after kidney transplantation.


Newer agents like tirzepatide, a long-acting GIP (glucose-dependent insulinotropic polypeptide) receptor and GLP-1 agonist, may have added efficacy but their use in kidney transplant patients has not been reported outside abstract presentations of small case series.

Conclusion

PTDM is a common post-transplant complication which affects many kidney transplant patients. It is essential for healthcare providers to remain vigilant in its diagnosis and management as we seek to improve long-term post-transplant outcomes. However, despite the availability of joint professional society guidelines from the ABCD-UKKA group

and expert consensus reports, challenges remain in day-to-day clinical practice due to the paucity of published evidence. The clinical challenges highlighted in this article (summarised in Figure 1) demonstrate the importance of multidisciplinary working between transplant and diabetes professionals to achieve the optimal outcomes for kidney transplant recipients at risk or who develop PTDM.

PTDM is a complex and multifactorial complication that requires an individualised approach to each kidney transplant patient. As kidney transplant recipients are high-risk candidates for development of PTDM, focusing clinical attention on prevention and/or optimised management of PTDM is essential as we strive to improve long-term survival, enhance quality of life, and ensure the longevity of transplanted kidney allografts. Continued research and the development of tailored therapeutic strategies will be key to addressing the clinical challenges presented by PTDM, ultimately improving the care of transplant recipients globally.

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