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ORIGINAL ARTICLE

WILEY

Peri-transplant glycaemic control as a predictor of pancreas transplant survival

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Abstract

Aims: The relationship between peri-transplant glycaemic control and outcomes following pancreas transplantation is unknown. We aimed to relate peri-transplant glycaemic control to pancreas graft survival and to develop a framework for defining early graft dysfunction.

Methods: Peri-transplant glycaemic control profiles over the first 5 days postoperatively were determined by an area under the curve [AUC; average daily glucose level (mmol/L) × time (days)] and the coefficient of variation of mean daily glucose levels. Peri-transplant hyperglycaemia was defined as an AUC ≥35 mmol/day/L (daily mean blood glucose ≥7 mmol/L). Risks of graft failure associated with glycaemic control and variability and peri-transplant hyperglycaemia were determined using covariate-adjusted Cox regression.

Results: We collected 7606 glucose readings over 5 days postoperatively from 123 pancreas transplant recipients. Glucose AUC was a significant predictor of graft failure during 3.6 years of follow-up (unadjusted HR [95% confidence interval] 1.17 [1.06-1.30], $P = .002$). Death censored non-technical graft failure occurred in eight (10%) recipients with peri-transplant normoglycaemia, and eight (25%) recipients with peri-transplant hyperglycaemia such that hyperglycaemia predicted a 3-fold higher risk of graft failure [HR (95% confidence interval): 3.0 (1.1-8.0); $P = .028$].

Conclusion: Peri-transplant hyperglycaemia is strongly associated with graft loss and could be a valuable tool guiding individualized graft monitoring and treatment. The 5-day peri-transplant glucose AUC provides a robust and responsive framework for comparing graft function.

KEYWORDS

glucose, glycaemic control, pancreas transplantation

Martin K. Rutter and David van Dellen contributed equally to this study.

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1 | INTRODUCTION

Pancreas transplantation is performed as part of the treatment strategy for patients with complex type 1 diabetes mellitus (T1DM). Primary function of the transplanted pancreas is assumed when glycaemic control improves towards normal values. The absence of an improvement in glycaemic control after reperfusion of the pancreas heralds justified concern about potentially catastrophic events resulting in early graft loss.^{1,2} Failure of the pancreas within the first 5 days is almost exclusively attributed to technical complications.²

In our experience, reactive investigation to severe hyperglycaemia post-transplantation seldom leads to graft salvage in cases of significant technical complications. At lower levels, glucose measurement acts as a physiological barometer of both the patient and the transplanted organs.³⁻⁵ The factors influencing hyperglycaemia in the early postoperative period are poorly defined, although it has been suggested that postoperative inflammation could mediate stress hyperglycaemia,⁵ pancreatic damage⁶ and possibly delayed graft function (DGF).

DGF is a poorly defined concept in pancreas transplantation and current definitions are based exclusively on the patient requirement for exogenous insulin (Table 1).⁷⁻¹² In these definitions, both the time-frame for the assessment post-transplant and the target glucose range that influence insulin initiation vary considerably. Consequently, there is no consensus on the definition of DGF, and reported rates of DGF vary considerably from 0%¹⁰ to 69%.⁷

The relationship between peri-transplant glycaemic control and outcomes is unknown. One reason for this might be because of inappropriate or an inadequate interpretation of glucose levels and trends. There is a tendency to interpret glucose levels either in isolation or as a trend within the context of a short period postoperatively. However, this short-term glucocentric approach has its limitations, i.e. (a) isolated random glucose levels have limited value because they may be explained by transient episodes of high metabolic stress after major surgery, and (b) glucose levels in isolation do not account for individual donor and recipient factors that could contribute to hyperglycaemia.

We hypothesized that peri-transplant glucose levels below those currently used to define graft dysfunction, predict subsequent pancreas transplant graft failure. Our aims were (a) to relate peri-transplant glycaemic control to pancreas graft survival, and (b) to develop a framework for defining early graft dysfunction, which is

based on glucose levels independently of insulin use, accounts for other causes of hyperglycaemia, predicts graft failure and enables treatment modification.

2 | METHODS

We analysed retrospective data from consecutive recipients of solid pancreas transplants performed from 2010 to 2015 in our programme.

2.1 | Routine practice

In our unit, all recipients of solid pancreas transplants underwent blood glucose measurement at 15-min intervals during the perioperative period starting immediately following reperfusion of the pancreas. Postoperatively, glucose measurements were performed hourly for the first 36 h. Thereafter, patients had their glucose levels measured on average seven times daily depending on the stability of glycaemic control, physiological parameters and postoperative recovery. Capillary blood glucose measurements were analysed using point of care analysers that were standardized and calibrated within a single critical care unit. Exogenous insulin therapy was routinely ceased once blood glucose levels dropped below 10 mmol/L. In patients who stopped exogenous insulin, blood glucose levels above 8 mmol/L prompted an urgent clinical review, including a surgical assessment on intensive care or the ward to identify the cause and treat any complications threatening graft viability. All patients followed a standardized steroid-free immunosuppression regimen, including induction with alemtuzumab, a calcineurin inhibitor and an anti-metabolite.

2.2 | Glycaemic control

Data from glucose readings were collected retrospectively from solid pancreas transplant recipients during the first 5 days postoperatively. The data were explored descriptively and the mean daily glucose levels were used for between-patient comparisons. We quantified the degree of glycaemic control from the area under the glucose level-time curve [AUC; average daily glucose level (mmol/L) × time (days)].

TABLE 1 Definitions and rates of pancreas delayed graft function (DGF) in the published literature

Lead author	Insulin requirement	Assessment day post-transplant	Glucose threshold, mmol/L	DGF rate
Troppman ⁷	≥30 units ≥15 units	5-10 11-15	<8.3	37/54 (69%)
Tan ⁸	Any regular dose ^a	Inpatient discharge	NA	176/531 (33%)
Maglione ⁹	Any regular dose	10	<8.3	16/87 (19%)
Qureshi ¹⁰	Any	7	NA	0/60 (0%)
Baitello ¹¹	Any	Inpatient discharge	NA	19/180 (11%)
Shin ¹²	>19 units	7	11.1	47/135 (35%)

Abbreviation: NA, not available.

^aMost patients requiring regular insulin required >10 IU daily.

Glycaemic variability was assessed using the coefficient of variation (CV), calculated as the standard deviation of average daily glucose levels/mean value over 5 days.

2.3 | Definitions

We defined normoglycaemia as a daily mean blood glucose of <7.0 mmol/L.¹³ We applied this normoglycaemia threshold to the AUC to define peri-transplant hyperglycaemia as an AUC ≥ 35 mmol/day/L over 5 days ($7 \times 5 = 35$). Pancreas graft failures were defined as a return to insulin dependence, and these were investigated in detail and the cause of failure confirmed either histologically or established from the medical notes. Technical failures of pancreas grafts were defined as failures due to portal vein thrombosis, anastomotic leak and bleeding. Kidney graft failures were defined as a return to dialysis dependence. Kidney graft function was determined by estimated glomerular filtration rate (eGFR).

2.4 | Parenteral nutrition

Gastroparesis is highly prevalent among the subset of patients with diabetes mellitus undergoing pancreas transplantation. Pancreas transplant recipients are at very high risk of malnutrition because of the combination of gastroparesis and postoperative ileus in the critical care setting. Consequently, early parenteral nutrition was considered for most patients during the study period and was adjusted according to each patient's weight. A 95-kg individual would receive 1500 mL of Triomel N4-GLE (Baxter Healthcare Ltd, Deerfield, Illinois, United States) over 24 h, which contains: calories, 1050 kcal; nitrogen, 6 g; glucose, 113 g; fat, 50 g; sodium, 31.5 mmol; potassium, 24 mmol; calcium, 3 mmol; magnesium, 3.3 mmol; phosphate, 12.75 mmol.

2.5 | Inflammatory mediators and C-peptide

In a subgroup ($n = 33$), serial blood samples were obtained at multiple time points over the first 3 days postoperatively (30 min after reperfusion and at 6, 12, 24, 48 and 72 h). Levels of circulating inflammatory mediators [tumour necrosis factor (TNF) α , interleukin (IL)-6, IL-10] were analysed using a DuoSet enzyme-linked immunosorbent assay kit (R&D Systems, Abingdon, UK). The lower limits of detection were TNF α 2 pg/mL, IL-6 1 pg/mL and IL-10 5 pg/mL. C-peptide was measured using a bioplex micro-array multi-bead based system (BioRad Life Science Group, Hercules, California, United States) for which the lower limit of detection was 1.0 pg/mL (331 pmol/mL).

2.6 | Data analysis

Demographic data from pancreas donors and recipients were first explored descriptively. Covariates with a significant relationship to postoperative glycaemic control (AUC) and variability (CV) were

identified using linear regression. Pancreas transplant recipients who returned to insulin dependence within the first 5 days because of technical failures ($n = 14$; explained below) were excluded from the survival analysis. Rates of graft failure were determined and risks of graft failure associated with peri-transplant hyperglycaemia (AUC ≥ 35), glycaemic control (AUC) and glycaemic variability (CV) were calculated using covariate-adjusted Cox regression. Linear regression assessed relationships between C-peptide, inflammatory mediators and glucose levels. Fisher's exact test determined the difference in rates of graft failure between recipients who experienced hyperglycaemia on day 0-1 versus those who did not.

Statistical analysis was performed using SPSS (Version 22.0; IBM SPSS Statistics for Windows, 2013 release; IBM Corp., Armonk, NY, USA). We calculated that our dataset would provide 86.1% power to detect a 10% reduction in graft failure using a two-way test when statistical significance was assumed at $P < .05$.

3 | RESULTS

Between 2010 and 2015, we collected 7606 glucose readings from 123 pancreas transplant recipients [male: 61%; mean \pm SD age 41 ± 9 years; body mass index (BMI) 24 ± 4 kg/m²] of which the majority (94%) had received a simultaneous kidney and pancreas transplant. Donors had a mean \pm SD age of 33 ± 13 years, BMI of 23 ± 3 kg/m², 55% were men, and 45% required insulin while on intensive care. Donors after brain death comprised 84% of the cohort.

3.1 | Glycaemic control

The mean \pm SD glucose levels on each day of the peri-transplant period were: day 0, 7.3 ± 2.0 mmol/L; day 1, 6.2 ± 1.3 mmol/L; day 2, 6.3 ± 1.2 mmol/L; day 3, 6.5 ± 1.1 ; and day 4, 6.7 ± 1.3 mmol/L. Over the duration of the first 5 days, the glucose AUC was 32.6 (4.3) mmol/day/L and glucose CV was 31 (18%). Normal glucose levels were maintained across the 5 days by 13 (12%) patients; 64 (59%) patients experienced hyperglycaemia on days 0 or 1 followed by normoglycaemia; and 32 (29%) patients experienced normoglycaemia on days 0 or 1 followed by transient hyperglycaemia between days 2 and 4 before achieving normoglycaemia again. In a subgroup ($n = 33$), median (IQR) AUC C-peptide levels were 161 (57-226) pmol h/L and were not related to either glucose AUC [β (SE) 0.003 (0.006); $P = .615$ nor glucose CV 0 (0); $P = .347$] (Table S1).

3.2 | Covariates

Donor and recipient variables associated with glycaemic control (AUC) and glucose variability (CV) were analysed (Table 2). Significant predictors of glucose AUC included donors after brain death [β coefficient (SE) 2.4 (1.1), $P = .032$], donor BMI [0.3 (0.1), $P = .047$], recipient BMI [0.3 (0.1), $P = .043$], and recipient parenteral nutrition, which did not include insulin [-3.4 (1.4), $P = .019$]. Total parenteral nutrition

TABLE 2 Baseline donor and recipient characteristics and their associations with average glucose levels (AUC) and average glucose variability (CV) during the first five postoperative days

Characteristic	Baseline values	Glucose AUC		Glucose CV	
		β coefficient (SE)	P value	β coefficient (SE)	P value
Donor					
Mean \pm SD age, years	33 \pm 13	0.53 (0.03)	.10	-0.002 (0.001)	.217
Male	60 \pm 54	-1.54 (0.83)	.07	0.04 (0.04)	.231
Mean \pm SD BMI, kg/m ²	23 \pm 3	0.25 (0.12)	.047	0 (0.005)	.963
Insulin use	46 \pm 41	-1.17 (0.84)	.17	0.04 (0.04)	.326
Donor type (DBD)	91 \pm 82	2.43 (1.11)	.032	0.07 (0.05)	.173
Recipient					
Mean \pm SD age, years	41 \pm 8	0.05 (0.05)	.335	-9×10^{-5} (0.002)	.966
Male	67 \pm 60	-0.37 (0.86)	.664	-0.1 (0.04)	.723
Mean \pm SD BMI, kg/m ²	24 \pm 4	0.26 (0.13)	.043	-0.01 (0.01)	.261
Parenteral nutrition (n = 76)	61 \pm 80	-3.35 (1.40)	.019	-0.03 (0.06)	.644
Mean \pm SD cold ischaemic time, min	715 \pm 197	0.001 (0.002)	.501	-5×10^{-5} (0.00)	.588

Note: Baseline values are n (%) unless stated.

Abbreviations: AUC, area under the curve for glucose concentration \times time during the first five postoperative days (mmol/day/L); BMI, body mass index; CV, coefficient of variation; DBD, donor after brain death; SD, standard deviation.

(TPN) was administered in 80% of patients. There were no significant covariates of glucose CV. When covariates were analysed according to the presence or absence of peri-transplant hyperglycaemia, there were no significant associations (Table S2).

3.3 | Graft failure prediction by peri-transplant glucose levels

Technical failures of pancreas grafts were seen in 14 patients, all of whom required exogenous insulin during the first 5 days. A further four patients required insulin within the first 5 days, but who did not experience technical failure of the pancreas graft, and were excluded from the analysis.

During a median follow-up of 3.6 years, graft failure occurred in 30 (24%) recipients. Causes of graft failure were established from a review of medical notes and, when appropriate, confirmed histologically (Table S3).

Non-technical graft failure occurring in transplant recipients (death-censored graft failure) occurred in eight (10%) with peri-transplant normoglycaemia and eight (25%) with peri-transplant hyperglycaemia (AUC \geq 35 mmol/day/L) such that the presence of hyperglycaemia predicted a three-fold higher risk of graft failure [HR (95% CI): 3.0 (1.1-8.0); $P = .028$; Log-Rank test $P = .021$; Figure 1]. These relationships remained statistically significant after adjusting for donor and recipient factors (Figure 2B). TPN did not affect the relationship between peri-transplant hyperglycaemia and graft failure [HR (95% CI) 4.39 (1.34-14.34), $P = .014$]. In an exploratory analysis adjusting for all potential covariates, peri-transplant hyperglycaemia was a significant predictor of graft failure [HR (95% CI) 5.15 (1.10-

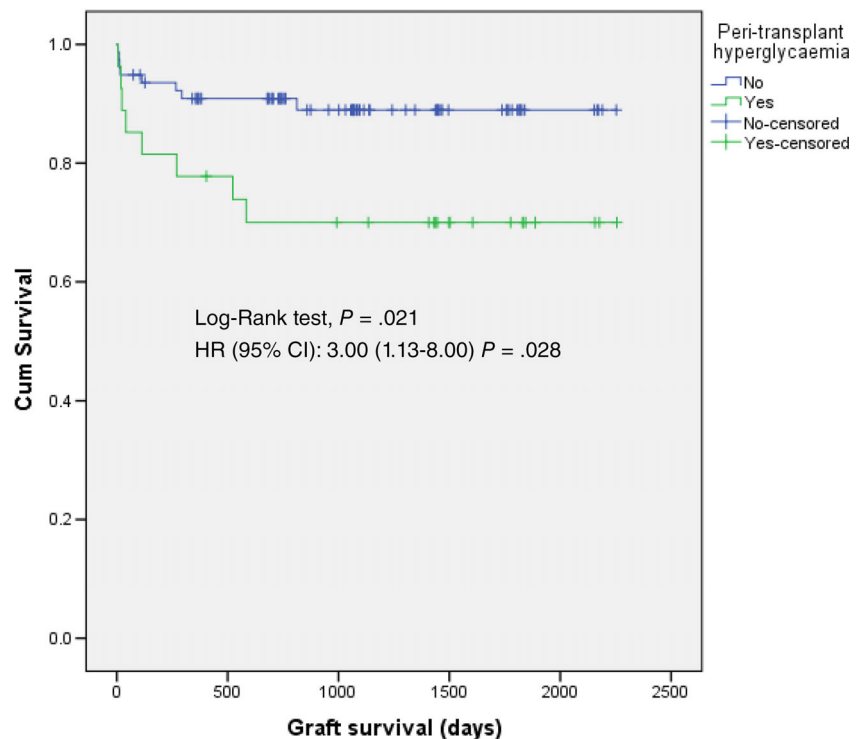
24.16), $P = .037$]. There was no difference in graft failure between recipients who experienced hyperglycaemia on day 0-1 [8 of 64 (14%)] versus those who did not [8 of 45 (18%), $P = .584$].

When considered as a continuous variable, glucose AUC was also a significant predictor of graft failure during 3.6 years of follow-up [unadjusted HR (95% CI) 1.17 (1.06-1.30), $P = .002$]. An overall 5 mmol/day/L higher glucose AUC (or 1 mmol/L higher mean glucose on each of the 5 days) was associated with an 85% higher risk of graft failure. Glucose AUC remained a significant predictor after adjusting for individual donor and recipient covariates (Figure 2A). TPN did not affect the relationship between glucose AUC and graft failure [HR (95% CI) 1.44 (1.01-1.28), $P = .033$]. In an exploratory analysis adjusting for all relevant covariates, glucose AUC was a significant predictor of graft failure [HR (95% CI) 1.25 (1.05-1.49), $P = .012$].

Higher glucose variability, assessed by the CV of glucose levels over 5 days, was not significantly related to the risk of graft failure during 3.6 years of follow-up [unadjusted HR: 2.49 (0.31-20.03), $P = .390$ for a unit higher value for CV].

There were 13 kidney graft failures during the study period, of which only two had experienced a concomitant pancreas graft failure. All cases of kidney graft failure were included in the analysis. Kidney graft failure was not related to glycaemic control [glucose AUC HR (95% CI) 1.05 (0.96-1.14), $P = .327$], glycaemic variation [glucose CV 1.00 (0.98-1.03), $P = .787$, or peri-transplant hyperglycaemia 1.31 (0.43-4.01), $P = .640$]. Kidney function was not related to glycaemic control [glucose AUC β (SE) 0.16 (0.45), $P = .720$], glycaemic variation [glucose CV -0.08 (0.13), $P = .551$], or peri-transplant hyperglycaemia [-6.27 (4.97), $P = .211$]. The non-significance of these data remained unchanged after adjusting for covariates.

FIGURE 1 Kaplan-Meier curves showing the survival probability stratified by peri-transplant hyperglycaemia (defined as glucose area under the curve >35 mmol/day/L). CI, confidence interval; HR, hazard ratio



3.4 | Inflammatory markers and C-peptide

Median (IQR) values for IL-6, IL-10, TNF α and C-peptide were 37.3 (29-75), 27.1 (16-52), 13.9 (6-34) and 65 (51-87) pg/mL respectively. As expected in the early postoperative phase, levels of inflammatory mediators were higher than normal values. There was no relationship between inflammatory mediators and glucose AUC (Table S4).

4 | DISCUSSION

The main findings in this study have shown that peri-transplant glycaemic control and hyperglycaemia over the first 5 days post-transplantation are strongly associated with graft loss. Indeed, modest changes in daily mean glucose levels are associated with considerable increases in the risk of graft failure. We have also demonstrated that peri-transplant hyperglycaemia occurs in the presence of a functioning graft and in the absence of a heightened inflammatory response. The latter are important negative findings, because they challenge the notion of DGF in pancreas transplantation based on existing definitions.^{7,8,10-12,14}

The study showed there was a paucity of published literature on peri-transplant glycaemic control in solid pancreas transplantation stems, in part, from the low numbers of pancreas transplants performed annually worldwide (approximately 2000). Consequently, an inadequate understanding of peri-transplant glycaemic control makes the definition of DGF a challenging concept with lack of uniform or robust adoption (Table 1).⁷⁻¹² For example, Tan et al.⁸ defined DGF by the recipient's need for any regular exogenous insulin at the time of hospital discharge; Maglione et al.⁹ defined DGF as any

requirement of insulin to maintain glucose levels <8.3 mmol/L at 10 days post-transplantation; meanwhile, Shin et al.¹² defined DGF as a total cumulative insulin requirement of ≥ 19 units within 7 days post-operatively to maintain a glucose level <11.1 mmol/L.

Existing definitions do not reflect pancreatic β -cell function per se but rather glycaemic control; function is best measured with C-peptide, ideally following a carbohydrate load. Mittal et al. performed an oral glucose tolerance test upon discharge from hospital at days 10-14 post-transplant (beyond the timeframe used by most definitions of DGF) and demonstrated the value of an abnormal oral glucose tolerance test (2-h glucose levels ≥ 7.8 mmol/L) in predicting graft failure at 3 years.¹⁵

No previous studies have analysed the relationship between glycaemic control and glucose variability measured over the peri-transplant period with graft survival. Rather, they have related outcomes to isolated or random glucose levels at ≥ 7 days post-transplantation. Our definition of peri-transplant hyperglycaemia, based on the 5-day peri-transplant mean daily glucose-time curve, predicts graft failure at glucose levels much below those used by other groups to define graft dysfunction. Moreover, we have shown that glucose levels assessed over the first 5 days predict graft failure in pancreas transplant recipients not requiring insulin during their hospital stay. We have previously reported data on peri-transplant glycaemic control in islet transplantation.¹⁶ Data from 10 512 glucose measurements during the first 5 days peri-transplant were analysed, although neither median glucose levels nor glucose CV predicted outcomes post-transplantation.

It remains unclear whether peri-transplant hyperglycaemia is a cause or a consequence, or both, of graft dysfunction in the transplanted pancreas in the peri-transplant period. Existing

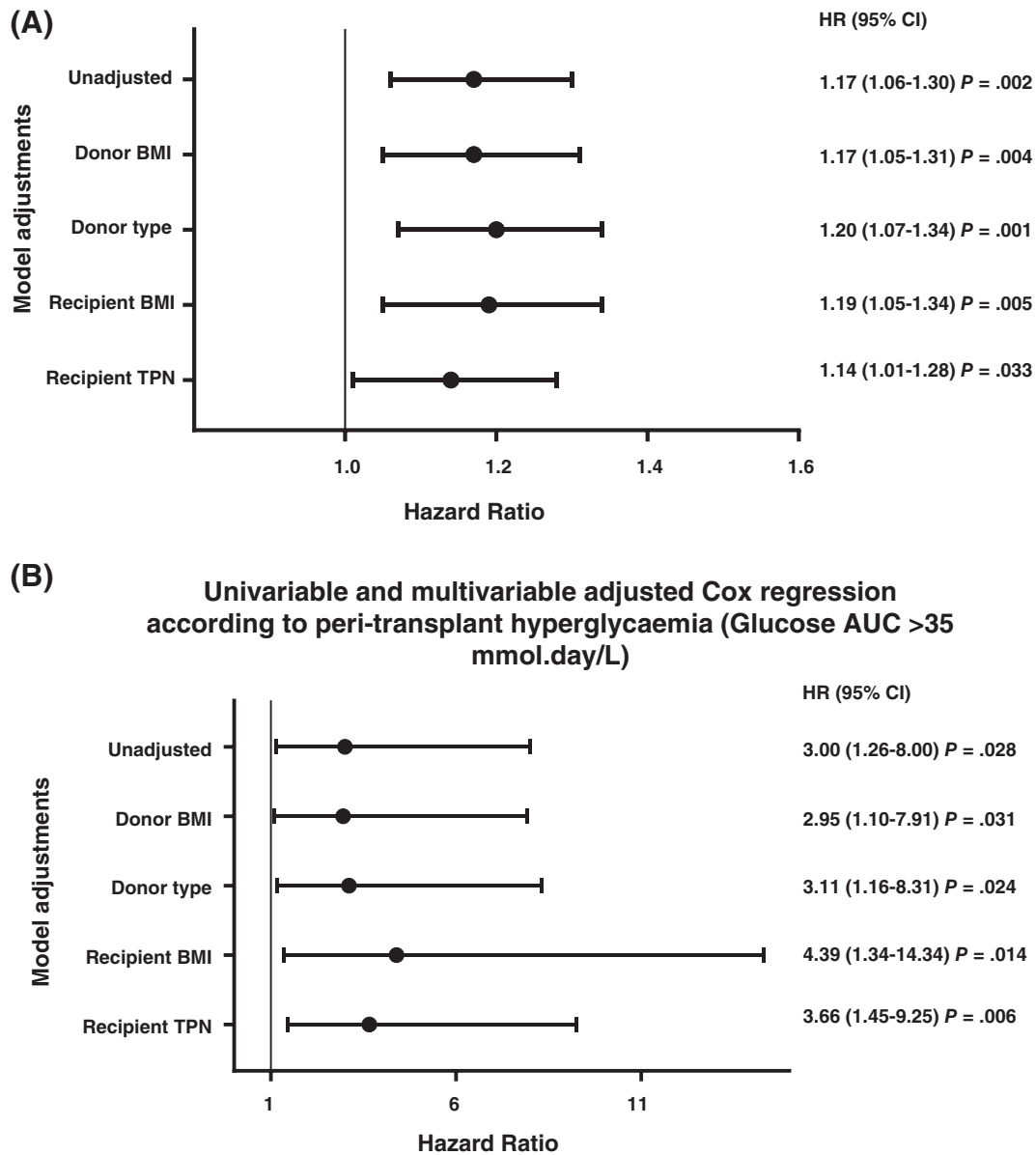


FIGURE 2 A, Univariable and multivariable-adjusted hazard ratios (HRs) for 3.6-year pancreas graft failure in relation to a unit higher average glucose level (AUC) during the first five postoperative days. B, Univariable and multivariable-adjusted HRs for 3.6-year pancreas graft failure in relation to peri-transplant hyperglycaemia (AUC >35 mmol/day/L) during the first five postoperative days. AUC, area under the curve; BMI, body mass index; TPN, total parenteral nutrition

definitions of DGF fail to account for other potential causes of hyperglycaemia in the recipient, such as insulin resistance in response to surgery,⁵ use of parenteral nutrition,¹⁷ as well as corticosteroid¹⁸ and immunosuppression therapies.¹⁹ Therefore, it may be argued that there is uncertainty whether peri-transplant hyperglycaemia is indicating graft dysfunction; although, if peri-transplant glucose levels predict longer-term graft failure then this might suggest the presence of graft dysfunction immediately post-transplant.

Other potential pathophysiological causes of graft dysfunction include donor quality, glucotoxicity,²⁰ and inflammation from brain death and during reperfusion.⁶ We did not identify any relationship between inflammation and peri-transplant glycaemic control nor

glycaemic variability. Donor age and BMI are widely recognized covariates that are strongly associated with both DGF and graft survival.^{8,9,12,21,22} This further highlights the inadequacies of current donor selection methodologies and absence of an objective assessment tool to describe pancreatic β -cell function in vivo in the donor and predict post-transplant function at the point of donor selection.²³

Hyperglycaemia causes oxidative stress and glucotoxicity. For pancreatic β -cells, this is a case of 'double jeopardy' because glucose-induced β -cell damage leads to higher glucose levels, which leads to further β -cell damage.²⁰ Insulin therapy is a well-recognized strategy, which can ameliorate glucotoxicity and promote β -cell rest in patients with diabetes.²⁴ However, this is more complicated in pancreas

transplantation because of the over-reliance on clinical feedback from glucose levels, perhaps inappropriately. In pancreatic islet cell transplantation, exogenous insulin therapy is continued during the peri- and post-transplant phases, in part, because islet function is delayed for at least 10 days after transplantation.²⁵ Peri-transplant insulin therapy is currently the standard of care in islet cell transplantation for this reason but also because its use is associated with higher rates of long-term insulin independence. Although, these data are far from conclusive, we can hypothesize that the benefits of insulin in this setting are in part because of β -cell rest induced in the recently transplanted cells.^{25,26} We might speculate that peri-transplant insulin therapy in solid pancreas transplantation could be doubly beneficial by ameliorating glucotoxicity and by providing β -cell rest during a period of heightened insulin resistance.

Hyperglycaemia during TPN use has been shown to be associated with increased hospital complications and mortality.²⁷ In our data, adjustment for TPN in the multivariable analysis did not alter the statistical significance of the relationship between either glycaemic control or peri-transplant hyperglycaemia and graft failure. TPN is a lipid-based emulsion and is known to exaggerate the inflammatory response and oxidative stress.²⁸ It is possible the hyperglycaemia secondary to TPN use will accentuate the effects of hyperglycaemia secondary to graft dysfunction. This could explain the stronger relationship between glucose AUC and graft failure.

Data on 5-day glucose AUC and peri-transplant hyperglycaemia provide an opportunity to stratify patients according to their risk of graft failure. Our single-centre results require replication in other cohorts but such stratification could enable individualized graft monitoring and treatment to reduce the risk of long-term graft failure. For example, immunosuppression regimens could be tailored to individual requirements by reducing the diabetogenic side effects of tacrolimus.^{19,29} In our study, patients did not receive insulin therapy for glycaemic control unless their blood glucose level exceeded 10.0 mmol/L in the absence of remediable graft complications. However, we speculate that patients who receive insulin to maintain a glucose level <7.0 mmol/L would have a better graft survival than patients who do not receive insulin and have higher mean daily glucose levels. Clinical trials will be needed to assess whether this individualized treatment could include peri- and post-transplant insulin therapy and/or oral hypoglycaemic therapies to improve long-term prognosis.

Our study has several strengths. First, we have a well-phenotyped cohort with high-quality data on exposures, outcomes and potential confounding factors. Second, use of serial glucose measurements over 5 days makes the glucose AUC a superior metric of glycaemic control compared with isolated random blood glucose levels. Glucose AUC boasts a number of advantages: it avoids using diagnostic labels, such as DGF, which cannot be validated in individual patients, and it may provide a standardized and comparable measure of function. This metric takes into account each glucose measure taken within the 5-day peri-transplant period. Small changes in

glucose levels have a cumulative daily risk associated with graft failure that is difficult to appreciate when glucose levels are reviewed in isolation. Our definition of peri-transplant hyperglycaemia, based on the 5-day glucose AUC, is both versatile regardless of individual centres' glucose thresholds for commencing post-transplantation insulin therapy.

One limitation of this study was the restriction of data to the first 5 days post-transplantation. Although we collected data, when present, from the first 7 days post-transplantation, the completeness of these data beyond 5 days was suboptimal. However, it is possible to extend the glucose AUC to include the first 7 days, and hence increase the AUC threshold for peri-transplant hyperglycaemia to 49 mmol/day/L. Nevertheless, extension of the definition to 7 days would require validation in a different dataset with complete data over this extended peri-transplant period. We acknowledge the potential value of a definition based on a 7-day period because the majority of pancreas transplants are performed simultaneously with a kidney transplant, and most definitions of DGF in kidney transplants are based on a 7-day period.^{30–32} Finally, we did not have access to continuous glucose monitoring at the time of the study. Continuous glucose monitoring is certainly feasible for future use in pancreas transplantation³ and could help strengthen the use of glucose AUC as a metric in pancreas transplantation.

5 | CONCLUSIONS

In conclusion, we have demonstrated that peri-transplant hyperglycaemia, determined by using the 5-day peri-transplant glucose AUC, predicts graft failure at glucose levels below those currently used to define graft dysfunction in recipients not receiving insulin. We have shown that peri-transplant hyperglycaemia occurs independently of good C-peptide production and inflammatory processes. Glucose AUC could be a valuable tool to guide individualized graft monitoring and treatment modification to reduce the impact of hyperglycaemia on graft outcome.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

IMS was involved in all aspects of the study and was lead author. ZLT contributed to the data collection and writing. RG was involved in the data collection and writing. HK contributed to the data collection, laboratory analysis, data interpretation and writing. AS was involved in all aspects of the study, but not data collection. CF contributed to the data analysis, statistical oversight and writing. PY was involved in the data collection, data analysis and writing. NAH contributed to the study concept and oversight, and writing. TA was involved in the study concept and oversight writing. MKR was involved in all aspects of the study and was a senior author. DvD contributed to all aspects of the study and was a senior author.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14181>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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