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ARTICLE

Postoperative impaired glucose tolerance is an early predictor of pancreas graft failure

Shruti Mittal · Myura Nagendran · Rachel H. Franklin · Edward J. Sharples · Peter J. Friend · Stephen C. L. Gough

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Abstract
Aims/hypothesis The management of pancreatic transplantation is limited by a lack of clinically relevant early markers of graft dysfunction to enable intervention prior to irreversible damage. The aim of this study was to assess the OGTT as an early predictor of pancreatic graft failure.
Methods Patients with graft failure (return to insulin dependence) were identified from a prospectively maintained clinical database. Data from OGTTs performed within 2 weeks of the transplant were retrospectively collected for 210 subjects, 42 with graft failure (21 after simultaneous pancreas–kidney transplant and 21 after isolated pancreas transplant) matched to 168 with functioning grafts. The groups were compared to assess the relationship between early OGTT result and pancreas graft failure.
Results Mean 2 h glucose from the OGTT was significantly higher in the overall graft failure group compared with the control group (8.36 vs 6.81 mmol/l, $p=0.014$). When interpreted in combination with fasting glucose, abnormal glucose tolerance was more common in the failed graft group (50% vs 22%, $p=0.001$). In an adjusted model, abnormal glucose tolerance emerged as the most predictive independent factor for graft failure, HR 1.66 (95% CI 1.22, 2.24), $p=0.001$. These findings were consistent between the different transplant procedures performed.
Conclusions/interpretation We conclude that early post-transplant abnormal glucose tolerance is associated with later whole organ pancreas graft failure. An OGTT performed within the first month postoperatively provides an easily measurable assessment of an independent early risk factor of pancreatic graft dysfunction.

Keywords Metabolic biomarkers · Pancreas transplant · Risk factors · Survival · Transplant outcome · Type 1 diabetes

Abbreviations
CIT Cold ischaemia time
IP Isolated pancreas transplant
SPK Simultaneous pancreas–kidney transplant

Introduction

Pancreas transplantation is an effective treatment for some people with type 1 diabetes, restoring insulin independence and offering significant quality of life and survival benefits [1]. Graft failure rates, defined as a return to insulin dependence, have been reduced, with graft survival rates reaching 89% for simultaneous pancreas–kidney transplant (SPK) and 82% for isolated pancreas transplant (IP) at 1 year and 71% and 58% at 3 years, respectively [1].

Peter J. Friend and Stephen C. L. Gough are joint senior authors.

S. Mittal (✉) · R. H. Franklin · P. J. Friend
Oxford Transplant Centre, Churchill Hospital, Old Street, Headington, Oxford OX3 7LE, UK
e-mail: shruti.mittal@gtc.ox.ac.uk

S. Mittal
Nuffield Department of Surgery, University of Oxford, Oxford, UK

S. Mittal · S. C. L. Gough
NIHR Oxford Biomedical Research Centre, Oxford, UK

M. Nagendran
Green Templeton College, University of Oxford, Oxford, UK

E. J. Sharples · S. C. L. Gough
Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK

E. J. Sharples · P. J. Friend
Nuffield Department of Medicine, University of Oxford, Oxford, UK

The long-term management of pancreas transplantation is complicated by the absence of a marker that enables graft dysfunction to be detected at an early enough stage to allow more intensive investigation or effective intervention. Previous studies investigating predictors of graft outcomes have focused on donor and recipient factors and short-term outcomes [2]. Whilst a number of studies have used the OGTT to monitor pancreas graft function [3, 4], only one has assessed the value of OGTT in predicting long-term graft function [5].

At the Oxford Transplant Centre, pancreas transplant recipients routinely undergo an OGTT post transplant, prior to discharge. We were, therefore, able to test the hypothesis that an OGTT performed within 14 days of whole organ pancreas transplantation, allows the identification of recipients at risk of later graft failure.

Methods

Donor and recipients were selected and allocated according to UK national procedures. Pancreas implantation was performed with systemic venous and enteric duct-drainage. All patients followed a steroid-free immunosuppression regimen of alemtuzumab followed by tacrolimus and mycofenolate mofetil maintenance therapy. All were free from medications for glycaemic control, including insulin, and underwent an OGTT prior to discharge at 10–14 days post transplant using 75 g oral glucose and blood sampling for serum glucose at 0 and 2 h. Normal glucose tolerance was defined according to WHO criteria (fasting glucose <6.1 mmol/l and 2 h glucose <7.8 mmol/l).

A prospectively maintained clinical database was searched to identify all pancreas transplants performed at the Oxford Transplant Centre between 2002 and 2011, which included 486 transplants during this period. Graft failure was defined as a return to insulin therapy for persistent hyperglycaemia. Patients who underwent pancreatectomy during the transplant admission or failed to achieve insulin independence were excluded. SPK and IP patients who were discharged with functioning pancreas transplants and did not require exogenous insulin but whose grafts subsequently failed were matched to a control group with ongoing graft function on a 1:5 and 1:3 basis, respectively. Cases were matched for year and type of transplant (SPK, pancreas transplant alone, pancreas after kidney, or second graft). Demographic, transplant related and outcome data were collected retrospectively.

SPSS software (IBM, Armonk, NY, USA, Version 20.0) was used for statistical analyses. For SPK and IP transplants, variables in the graft failure group were compared with those in the control group (using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables). Cox regression analysis was performed to test for associations between variables and graft outcome. The model was adjusted for type of transplant. Significant variables were added into a multivariate model to identify independent predictive factors. Pancreas graft survival was compared for significant variables using Kaplan–Meier survival analysis.

Results

Demographic data In total, 54/486 recipients were identified as having suffered pancreas graft failure, of which 12 recipients were excluded based upon early pancreatectomy following graft pancreatitis or surgical complications. The remaining 42 graft failures included 21 SPK transplants and 21 IP transplants, and were matched to 105 and 63 recipients with ongoing pancreas graft function, respectively, for year and type of transplant. In total, 210 graft recipients were included in the analysis. Data were censored at time of death or duration of follow-up (8–115 months, median 30 months). Transplants where graft failure occurred were comparable to those with ongoing graft function in terms of donor and recipient characteristics, although the cold ischaemia time (CIT) was longer in the failure group vs the functioning graft group. Although not significant, there also appeared to be fewer female

Table 1 Comparison of baseline characteristics for failed pancreas grafts vs grafts with ongoing function

Characteristic	Failed grafts (n=42)	Functioning grafts (n=168)	p value
Time of failure (months)	8 (1–53)		
Operation type			
SPK	21 (50.0)	105 (62.5)	
PTA	13 (31.0)	41 (24.4)	
PAK	6 (14.3)	15 (8.9)	
PASPK/PAPTA	2 (4.8)	7 (4.2)	0.320
Recipient sex, n (%) female	12 (28.6)	81 (48.2)	0.058
Recipient age (years)	41.46±7.39	43.59±9.85	0.190
Donor age (years)	36.49±12.70	36.50±13.42	0.995
Donor BMI (kg/m^2)	24.25±3.33	23.89±3.70	0.586
Donor type (DCD)	10 (23.8)	24 (14.2)	0.079
CIT (min)	753.00±158.13	672.21±172.43	0.016
Tacrolimus level (μg/l)	11.11±5.17	9.98±4.99	0.203
OGTT result, 0 min (mmol/l)	5.30±0.93	5.61±1.01	0.056
OGTT result, 120 min (mmol/l)	8.36±3.82	6.80±SD 2.10	0.014
Abnormal OGTT result	21 (50)	40 (23.8)	0.001
Kidney rejection	7 (33.3)[a]	8 (7.6)[a]	<0.001
Kidney failure	9 (42.9)[a]	5 (4.8)[a]	<0.001

Values are presented as n (%), mean±SD or median (range)

[a] Percentage of total SPK in each group

DCD, donor after circulatory death PASPK, pancreas after SPK; PAPTA, pancreas after PTA; PTA, pancreas transplant alone

Table 2 Cox regression and Kaplan–Meier survival curve adjusted for transplant type

Variable	HR	95% CI	*p* value
Recipient sex (F)	0.518	0.259, 1.035	0.063
Recipient age	0.978	0.943, 1.014	0.232
Donor age	1.008	0.984, 1.032	0.522
Donor BMI	1.045	0.959, 1.140	0.317
Donor type (DBD)	0.730	0.354, 1.505	0.394
CIT (min)	1.002	1.000, 1.004	0.021
Sensitisation	1.217	0.786, 1.883	0.379
Tacrolimus level	1.044	0.989, 1.101	0.119
OGTT result, 0 min	1.301	1.029, 1.646	0.028
OGTT result, 120 min	1.207	1.099, 1.325	<0.001
Abnormal OGTT result	1.655	1.221, 2.243	0.001

DBD, donor after brain death

recipients in the failed graft group (Table 1). Subgroup analyses showed the difference in CIT was significant in the IP group only (800 vs 683 min, $p=0.010$), and the sex difference was driven by a notably low percentage of female recipients in the failed SPK group (9.5% vs 31.4%, $p=0.031$). Neither pre-transplant insulin doses nor tacrolimus immunosuppression levels at the time of the OGTT differed between the groups (data not shown).

Metabolic outcomes The mean 2 h post-OGTT serum glucose level was statistically higher in the failure group vs the functioning group ($p=0.014$). When analysed in combination with fasting glucose, the diagnosis of abnormal glucose tolerance (according to the WHO criteria [6]) was significantly more common in the failed graft group ($p=0.001$; see Table 1). Subgroup analysis showed this finding to be consistent in both the SPK and IP groups, with abnormal OGTT carrying greater significance than 2 h glucose alone.

The early OGTT had low sensitivity (47.6% SPK, 52.4% IP) but high specificity (79.1% SPK, 73.0% IP) for identifying graft failure, with a negative predictive value of 88.3% for SPK and 82.1% for IP. A univariate Cox regression analysis adjusted for transplant type showed CIT, 0 h serum glucose, 2 h serum glucose and an abnormal OGTT to be predictive of graft failure, with abnormal OGTT showing the highest predictive power (HR 1.66, CI 1.22, 2.24; $p=0.001$) (Table 2). In a multivariate model, although CIT and OGTT results showed an interaction effect, they both emerged as independent predictive factors.

Graft survival According to Kaplan–Meier analysis, recipients with early abnormal glucose tolerance had significantly poorer graft survival compared with those with normal glucose tolerance (for SPK: 1 year survival: 78% vs 97%, 3 year survival 66% vs 86%, logrank $p=0.008$; for IP: 1 year survival 74% vs 87%, 3 year survival 55% vs 79%, logrank $p=0.029$, Fig. 1). Of 153 recipients with normal glucose tolerance, 21 (13.7%) suffered pancreas graft failure, with a median time to graft loss of 12 months; of 40 recipients with impaired glucose tolerance, 14 (35.0%) failed, with a median time to graft loss of 7 months; of 17 recipients with WHO-defined diabetes (but insulin independent), seven (38.9%) failed, with a median time to graft loss of only 4 months post transplant. Neither kidney graft rejection (18.8% vs 9.65%, $p=0.206$) nor kidney failure (12.5% vs 10.6%, $p=0.752$) was statistically greater in recipients who displayed abnormal glucose tolerance vs those with normal glucose tolerance; however, the kidney rejection rate was numerically higher.

Discussion

We have shown, for the first time, that abnormal glucose tolerance early after pancreas transplantation is associated with a higher risk of later pancreas graft failure, and that recipients showing the greatest degree of early glucose intolerance have the shortest time to graft failure. We have shown that this association is consistent for both SPK and IP transplants and is independent of demographic factors thought to influence graft outcome. We have also shown that normal glucose tolerance post transplant is associated with a 3 year graft survival of around 86% and that the OGTT has a high negative predictive value. Thus, an early normal result can be considered reassuring of good long-term graft survival.

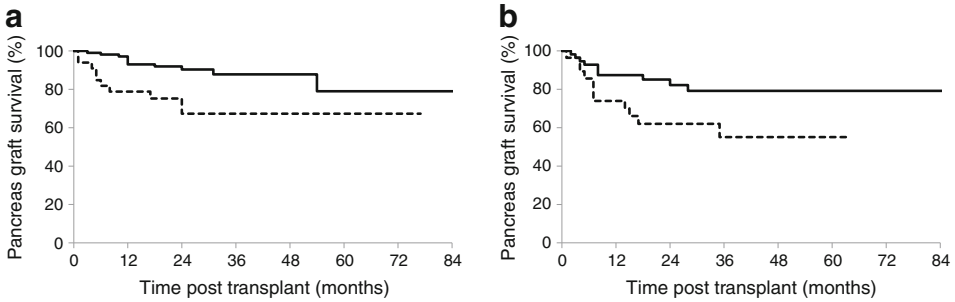

Fig. 1 Kaplan–Meier survival curve of pancreas graft survival for (**a**) SPK and (**b**) IP. Solid line, normal glucose tolerance; dashed line, abnormal glucose tolerance

Previous attempts to identify predictors of graft failure have focused on donor factors and registry data, allowing identification of high-risk donors and informing organ selection and allocation [2, 4]. They are however, of limited use when predicting either graft outcome from non-high-risk donors, or individual long-term graft outcomes. Additionally, following the decision to accept an organ for transplantation, there are no robust postoperative measures to identify grafts at risk of failure.

A previous study has shown poorer long-term graft survival with a higher mean glucose on 24 h glucose profiling at 1 year post transplant in 53 SPK recipients [7]. Additionally, shorter graft survival with impaired glucose tolerance in 41 recipients 1.7±1.7 years post transplant has been reported. The present study, conducted in a much larger cohort, with a mean duration of follow-up of 30 months has the advantage of utilising an accessible test at an early time-point, and thus greater potential clinical utility, since the greatest return to exogenous insulin occurs in the first year post transplant.

Although CIT and recipient sex emerged in this study as significant factors, unlike an abnormal OGTT result, this was not consistent in both SPK and IP groups. It is interesting to note that CIT showed statistical interactions with an abnormal OGTT result, since this may represent graft damage as a result of ischaemia–reperfusion injury, which correlates with increased CIT. The reason for the disproportionately low number of female SPK recipients suffering graft failure is not clear and may simply represent a random finding resulting from small numbers. Although it is possible to speculate that this difference is related to better treatment compliance in female recipients, there was no evidence to support this in the current study.

The mechanism underlying the relationship between early graft dysfunction and an increased risk of later failure is unknown. It may represent reduced functional beta cell mass at the time of implantation as a result of trauma, or may represent the temporary effects of ischaemia–reperfusion injury, commonly seen in kidney transplantation as delayed graft function. Delayed pancreas graft function, currently defined as the need for exogenous insulin at the time of discharge, has not, however, been associated with poorer long-term pancreas graft survival [8]. The use of therapies to increase insulin secretion, such as incretin hormones, or exogenous insulin itself may be of benefit in abnormal glucose tolerance.

The authors recognise the study limitations. First, there are inherent limitations associated with retrospective analyses, including collection bias associated with missing data. The present study does, however, benefit from detailed single-centre data and does not suffer from bias introduced by heterogeneous immunosuppression protocols and post-transplant management of registry data. Second, IP transplantation is less commonly performed and a smaller cohort was available for analysis compared with the SPK group, which limited the achievable matching ratio. Nevertheless, combining the groups showed no significant differences, and subgroup analyses confirmed that associations and significances remained in both groups. Third, graft failures secondary to surgical complications or early pancreatectomy following sepsis were excluded as glucose tolerance may be altered by these confounding factors. Whilst the exclusion of these individuals allows for more meaningful interpretation of the data in an important group, our findings may not apply in the context of sepsis and should only be considered relevant to recipients considered to have good graft function 2-4 weeks post transplant. Fourth, type 1 diabetes is often associated with abnormalities of glucose homeostasis many months prior to diagnosis [9]. Longitudinal data may better reflect the complex post-transplant environment, comprising autoimmunity, alloimmunity and the inflammatory manifestations of ischaemia—all of which may contribute to the pathogenesis of beta cell destruction. Future prospectively planned studies should, therefore, include detailed assessments of insulin secretion and sensitivity along with measures of immunological function and inflammation to provide insights into the pathology of graft failure.

In conclusion, we have shown that an early postoperative OGTT may help define those recipients discharged with functioning grafts not requiring exogenous insulin who are high risk for all-cause future graft failure. This early surrogate for graft survival has the potential to direct close surveillance and targeted management aimed at preserving graft function.

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