Insulin independence following islet transplantation improves long-term metabolic outcomes

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RESEARCH ARTICLE

Insulin independence following islet transplantation improves long-term metabolic outcomes

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Abstract

Aims: Pancreatic islet allotransplantation is an effective therapy for type 1 diabetes mellitus, restoring glycaemic control and hypoglycaemic awareness in patients with recurrent severe hypoglycaemia. Insulin independence following transplant is being increasingly reported; however, this is not a primary endpoint in the UK. Having surpassed 10 years of islet transplantation in Scotland, we aimed to evaluate the impact of insulin independence following transplant on metabolic outcomes and graft survival.

Methods: We conducted a retrospective analysis on data collected prospectively between 2011 and 2022. Patients who underwent islet transplantation in Scotland up to the 31st January 2020 were included. Primary endpoint was graft survival (stimulated C-peptide >50 pmol/L). Secondary endpoints included GOLD score, HbA1c, C-peptide and insulin requirement. Outcomes were compared between patients who achieved insulin independence at any point following transplant versus those who did not.

Results: 60 patients were included. 74.5% experienced >50 severe hypoglycaemic episodes in the year preceding transplant. There was a 55.0% decrease in insulin requirement following transplant and 30.0% achieved insulin independence. Mean graft survival time was 9.0 years (95% CI 7.2–10.9) in patients who achieved insulin independence versus 4.4 years (95% CI 3.4–5.3) in patients who did not. Insulin independence was associated with significantly improved graft function, glycaemic control and hypoglycaemic awareness at 1 year.

Conclusions: This is the largest UK single-centre study on islet transplant to date. Our findings demonstrate significantly improved outcomes in patients who achieved insulin independence following islet transplantation.

KEYWORDS

C-peptide, Diabetes Mellitus, Type 1, graft survival, hypoglycaemia, insulin, Islets of Langerhans, Islet Transplantation

1 | INTRODUCTION

Diabetes mellitus affects 537 million people worldwide and is a major cause of premature mortality.[1] Type 1 diabetes mellitus (T1DM) accounts for 10% of diabetes diagnoses and results in the immediate and lifelong requirement for daily exogenous insulin.[2] T1DM is precipitated by the autoimmune destruction of pancreatic β-cells in the Islets of Langerhans, leading to a deficiency in endogenous insulin and loss of glycaemic control.[3] The main complication of insulin therapy in T1DM is recurrent hypoglycaemia, which results in impaired hypoglycaemic awareness.[4] Severe hypoglycaemia (SH) is a major complication of T1DM, with a prevalence of up to 40%.[5] T1DM-related complications result in significant morbidity, mortality and healthcare costs.[6]

Many technologies have been developed to manage T1DM, including continuous or flash glucose monitoring, insulin pumps and automated insulin delivery systems.[7] Most of these aim to enhance blood glucose monitoring or the administration of exogenous insulin. Pancreatic islet allotransplantation provides an effective alternative, restoring hypoglycaemic awareness, glycaemic control and leading to a period of insulin independence in many patients.[4,8,9]

While there are data to suggest poorer outcomes from islet transplantation compared to solid organ pancreas transplantation, defined by insulin independence rates,[10] solid organ transplant is often contraindicated in patients with comorbid cardiovascular disease.[8] Islet transplantation is a minimally invasive form of β-cell replacement therapy and offers an alternative use for pancreata that may be unsuitable for whole organ transplantation.[8]

1.1 | History

The first reported attempt at islet transplantation was in 1893, with the subcutaneous injection of ovine pancreatic tissue into a 15-year-old boy with Diabetic Ketoacidosis in Bristol (UK), who died 3 days later.[11] Few further attempts in humans were documented until the late 20th century. *Najarian* et al. conducted the first series of clinical islet transplants in 1977.[12] All patients remained dependent on exogenous insulin following transplant. The first reported case of insulin independence following islet transplantation was in 1978 in Switzerland.[13] Islets were embolised into the spleen of a patient with C-peptide negative T1DM, who achieved insulin independence by 1 year following transplant. Many centres began to replicate the islet transplant procedure. However, between the 1970s and 2000, fewer than 10% of patients on the islet transplant registry maintained insulin independence for longer than a year on steroid-based immunosuppression regimens and clinical outcomes remained poor.[9,14]

In 2000, *Shapiro* et al. published the Edmonton Protocol.[15] This protocol involved infusing high-quality islet isolations using novel techniques and a steroid-free immunosuppression regimen. Insulin independence was achieved in seven consecutive patients and favourable metabolic outcomes were observed. The protocol has been adopted by many centres around the world and has led to insulin independence rates of up to 50%–79% and improved patient outcomes.[8,9,16] Insulin independence has since become increasingly reported in the literature.[9,17]

Insulin independence is not currently a primary endpoint in the United Kingdom, and many centres aim purely for adequate glycaemic control even if insulin independence is not achieved, primarily due to limited graft availability.[10] There is a lack of randomised controlled trial data and outcome measures are not consistently reported in the literature.[9,18] While infused islet mass is the most frequently reported primary outcome, research highlights the significance of non-yield-based endpoints in predicting graft function and patient outcomes.[18]

What is already known?

- Islet transplantation is an effective therapy for complicated type 1 diabetes mellitus.
- Insulin independence is becoming increasingly reported as an outcome measure following transplant but this is debated.

What this study has found?

- Insulin independence following transplant results in significantly improved graft survival and metabolic outcomes.

What are the implications of this study?

- Our findings suggest favourable outcomes in patients who achieve insulin independence.
- We would recommend further research into the use of insulin independence as an outcome measure of islet transplantation.

1.2 | Aims

Following the 10th anniversary of the Scottish National Islet Transplant Programme in 2021, our study aimed to evaluate the impact of insulin independence on graft survival and metabolic outcomes following islet

transplantation in Scotland. The Scottish National Islet Transplant Programme is the largest in the UK and one of the most active worldwide. This analysis represents the largest UK single-centre study of its kind.

2 | METHODS

2.1 | Study design

We conducted a retrospective database analysis on data collected prospectively since the conception of the Scottish National Islet Transplant Programme in 2011. We included patients who underwent pancreatic islet allotransplantation in Scotland up to and including 31st January 2020, to allow a minimum of 2 years of follow-up. Pre-transplant recipient characteristics included sex, age, BMI, daily insulin requirement, HbA1c, GOLD score and SH incidence. SH was defined, according to the American Diabetes Association (ADA), as hypoglycaemia requiring the assistance of another person to administer resuscitative measures.[19] SH incidence was quantified up to 50 events per year or recorded as '>50'. HbA1c was reported using both the IFCC (mmol/mol) and the DCCT (%) units. We also recorded donor status, infused islet mass, purity and viability of the first transplant. Donor status was defined as either Donation after Brainstem Death (DBD) or Donation after Circulatory Death (DCD). Mixed Meal Tolerance Tests (MMTTs) were conducted at 1, 3, 6 and 12 months following transplant and 6 monthly thereafter. Patients were fasted overnight before appointments. C-peptide, insulin and glucose were recorded before and at 90 minutes following a 40 g carbohydrate load (150 mL Fortisip Compact). Also recorded at each appointment were HbA1c, GOLD score, daily insulin requirement, BETA-2 Score and SH incidence. Follow-up data were analysed up to and including 31st January 2022. The South East Scotland Research Ethics Service deemed this study not to require ethical review as this was routinely collected clinical data, anonymised prior to analysis.

The primary endpoint was graft survival, defined as 90-minute C-peptide >50 pmol/L at follow-up MMTTs. Secondary endpoints were HbA1c, C-peptide, GOLD Score, BETA-2 Score, Daily insulin requirement and SH incidence. Outcomes were compared between those who achieved insulin independence at any point following transplant versus those who never achieved insulin independence.

All islet transplant procedures were conducted at the Royal Infirmary of Edinburgh. Patients were fasted for 2 h before and 4 h after the procedure. Etanercept and an induction agent (Alemtuzumab or Basiliximab) were administered on the ward before transplant. The procedure was performed under light sedation, local anaesthetic and pain relief. Following transplantation, patients were commenced on a steroid-free immunosuppression regimen consisting of Mycophenolate Mofetil and Adoport (Tacrolimus). All patients were consented for transplant before listing and on the day of the procedure. The majority of patients were anticipated to achieve two islet infusions. If a patient achieved clinically significant graft function following one infusion, a second infusion was not indicated. A third islet infusion was indicated in the absence of clinically significant graft function.

2.2 | Statistical analysis

Data were reported as median (IQR) for continuous data and n (%) for categorical data. Mean graft survival duration was compared between groups (significance level $\alpha = 0.05$) with 95% confidence intervals (CI). Kaplan–Meier survival curves were used to compare cumulative survival from the first transplant. Data were censored for patients with a functional graft at the end of their available follow-up. Independent Samples *T*-Tests were used to compare metabolic outcomes at 1 year following the initial transplant (significance level $\alpha = 0.05$). To test for normality, we plotted histograms with normal lines for each continuous outcome variable within the independent and dependent groups. We then used the Shapiro–Wilk test of normality to test the null hypothesis that data came from normally distributed populations. Data were normally distributed in all groups. Pearson's chi-squared test was used to test for associations between pre-transplant variables and insulin independence following transplant in order to identify potential explanatory variables. Statistical analysis was conducted using *IBM SPSS® Statistics version 24.0*.

3 | RESULTS

A total of 61 patients underwent pancreatic islet allotransplantation between February 2011 and January 2020. One patient declined follow-up and data were collected for the remaining 60. Median age was 49.0 years (40.0–53.0). Median daily insulin requirement before transplant was 0.5 units per kg (0.4–0.6). Median HbA1c was 61 mmol/mol (51–71) (7.7% [6.8–8.6]) and GOLD score was 7.0 (6.0–7.0). 74.5% of patients experienced >50 SH events in the year before transplant. 82.0% of donors were defined as DBD and 18.0% DCD. Median donor age was 47.0 years (36.0–53.0). Median islet mass per kg infused was 4300.0 (3600.0–6200.0) with a viability of 89.0% (84.0–93.0) and purity 83.0% (74.0–90.0). 20.0% ($n = 12$) of patients received 1 islet infusion, 76.7%

($n=46$) received 2 and 3.3% ($n=2$) received 3 infusions. There was a 55.0% reduction in median insulin requirement 1 month following the initial transplant. 30.0% ($n=18$) of patients achieved insulin independence. There were no deaths at any time post-transplant in our sample. Table 1 shows the pre-transplant patient and islet infusion-related variables.

3.1 | Metabolic outcomes at 1 year

Median 90-minute C-peptide at 1 year was 484.0 pmol/L (223.0–675.5) in the insulin-dependent group. This was significantly increased at 877.5 pmol/L (446.0–1426.3) in the insulin-independent group ($p=0.0009$). HbA1c was 54 mmol/mol (48–66) (7.1% [6.5–8.2]) in the dependent group and 50 mmol/mol (37–55) (6.7% [5.5–7.2]) in the independent group ($p=0.0256$), demonstrating significantly improved glycaemic control. There was also a significantly reduced GOLD score in the independent group of 1.0 (1.0–4.0) compared to 4.0 (2.0–7.0) in the insulin-dependent group ($p=0.0415$). BETA-2 Score was 3.9 (2.6–8.7) in the DEP group and 6.4 (3.2–18.7) in the IND group ($p=0.0147$). There was no significant difference in daily insulin requirement between groups. 88% of patients were free from SH at 1 year. Data were normally distributed for all metabolic outcomes measured. Data are illustrated in Table 2.

The cumulative incidence of severe hypoglycaemia relapse (the occurrence of at least one SH event since transplant) was 46.6% at 5 years post-transplant (Figure 2). The mean duration free from any SH events was 3.4 years (95% CI 2.9–4.0). There was no significant difference between the insulin-independent and insulin-dependent groups.

3.2 | Long-term graft survival

Mean overall graft survival time was 7.0 years (95% CI 5.6–8.4). The cumulative 10-year graft survival was 52.6%. Mean graft survival time in the insulin-dependent group was 4.4 years (95% CI 3.4–5.3), and in the insulin-independent group was 9.0 years (95% CI 7.2–10.9). Figure 3 shows Kaplan–Meier curves of graft survival overall (A) and stratified by insulin independence (B).

3.3 | Pre-transplant predictors for insulin independence

Of the pre-transplant infusion and patient characteristics recorded, insulin requirement per kg was the only variable

TABLE 1 Pre-transplant patient and islet infusion-related variables.

	Total population	DEP	IND	*p* value
Patient characteristics				
Sex				0.72
Male	25 (42.4)	18 (43.9)	7 (38.9)	–
Female	34 (57.6)	23 (56.1)	11 (61.1)	–
Age at 1st Transplant, years	49 (40–53)	49 (40–54)	50.5 (38–53.3)	0.46
BMI, kg/m^2	26.4 (23.7–29.3)	26.4 (23.5–30)	26.3 (23.9–27.7)	0.36
Daily insulin, units per kg per day	0.53 (0.37–0.62)	0.57 (0.43–0.63)	0.47 (0.34–0.58)	0.04
HbA1c				
mmol/mol	61 (51–71)	61 (53–74)	60 (49–69)	0.21
%	7.7 (6.8–8.6)	7.9 (7.1–9)	7.7 (6.7–8.5)	0.20
GOLD score	7 (6–7)	7 (6–7)	6.5 (5.3–7)	0.13
Infusion characteristics				
Donor status				0.97
DBD	49 (83.1)	34 (82.9)	15 (83.3)	–
DCD	10 (16.9)	7 (17.1)	3 (16.7)	–
IEQ per kg body weight, Units×1000	4.3 (3.6–6.2)	4.2 (3.7–6.6)	4.9 (3.5–6.1)	0.17
Purity, %	83 (74–90)	85 (75–90)	80 (72.3–90)	0.20
Viability, %	89 (84–93)	89 (83.5–92.5)	90 (84.3–96)	0.34

Note: Data are *n* (%) or median (IQR) unless otherwise stated. IEQ = islet equivalents. *p* values correspond to insulin-independent (IND) versus insulin-dependent (DEP) groups.

TABLE 2 Metabolic outcomes 1 year following transplant.

	ALL ($n=60$)	DEP ($n=42$)	IND ($n=18$)	p value
HbA1c	54 mmol/mol (46–62)	54 mmol/mol (48–66)	50 mmol/mol (37–55)	0.0256
	7.1% (6.4–7.8)	7.1% (6.5–8.2)	6.7% (5.5–7.2)	
90 min C-peptide (pmol/L)	560.0 (245.0–877.5)	484.0 (223.0–675.5)	877.5 (446.0–1426.3)	0.0009
GOLD score	3.0 (1.0–7.0)	4.0 (2.0–7.0)	1.0 (1.0–4.0)	0.0415
Daily Insulin Req (IU/kg)	0.2 (0.1–0.4)	0.3 (0.1–0.4)	0.1 (0.0–0.4)	0.1057
BETA-2 score	5.0 (2.7–10.7)	3.9 (2.6–8.7)	6.4 (3.2–18.7)	0.0147

Note: Data are Median (IQR). p values correspond to insulin-independent (IND) versus insulin-dependent (DEP) groups.

statistically different between samples. Lower insulin requirement, 0.5 IU/kg (0.3–0.6) compared to 0.57 IU/kg (0.43–0.63), was associated with insulin independence post-transplant ($p=0.04$). There were no other significant differences between samples amongst the variables recorded (sex, age, BMI, HbA1c, GOLD score, donor status, infused islet mass, purity, viability), Table 1.

4 | DISCUSSION

Our findings demonstrate significantly improved glycaemic control and hypoglycaemic awareness at 1 year post-transplant in patients who achieved insulin independence compared to those who did not. HbA1c at 1 year post-transplant indicated improved glycaemic control in the IND group, 50 mmol/mol (6.7%), compared to the DEP group, 54 mmol/mol (7.1%). BETA-2 score estimates graft function as a continuous variable.[20] BETA-2 score indicated improved graft function in the IND group, 6.4 (3.2–18.7) compared to the DEP group, 3.9 (2.6–8.7) ($p<0.05$). Mean overall graft survival duration was 7.0 years with a cumulative graft survival of 52.6% at 10 years, demonstrating good long-term graft function. Graft survival duration was significantly increased in the insulin-independent group (9.0 years), an average of 4.7 years longer than the insulin-dependent group (4.4 years).

The Igls criteria, developed by the International Pancreas and Islet Transplant Association (IPITA) and the European Pancreas and Islet Transplant Association (EPITA) in 2017 (Igls, Austria), define 'good graft function' according to 4 criteria[21]:

1. Reduction in insulin requirement >50.0%.
2. HbA1c <7.0% (53 mmol/mol).
3. Resolution of severe hypoglycaemia.
4. Clinically significant graft function.

The insulin-independent study group achieved all four criteria at 1 year following the initial transplant. In contrast, patients who remained insulin-dependent following transplant had an HbA1c of 54 mmol/mol (48–66) (7.1% [6.5–8.2]) and graft function was significantly lower than in the insulin-independent group 1 year following transplant. GOLD score ≥4.0 indicates impaired hypoglycaemic awareness.[22] While GOLD score was significantly improved in both groups following transplant (Figure 1b), impaired hypoglycaemic awareness was observed in the insulin-dependent group at 1 year, GOLD score 4.0 (2.0–7.0), while the mean GOLD score in the insulin-independent group was significantly reduced at 1.0 (1.0–4.0) ($p=0.0415$) indicating improved hypoglycaemic awareness.

Figure 1 demonstrates a gradual decline in C-peptide production between 1 and 3 years post-transplant, before reaching a plateau (A). As would be expected, this corresponds to an increase in HbA1c (and relative loss of glycaemic control) over this period (B). It would also have been useful to plot SH incidence more accurately across this period in order to provide further clinical correlation, however this was not possible due to the data available. The cumulative incidence of SH relapse (defined as ≥1 SH event since transplant and therefore not the true SH incidence) is shown in Figure 2, indicating a gradual increase in SH relapse in the years following transplant.

Our results reflect the positive metabolic outcomes observed following islet transplant in the literature. There was a similar reduction in insulin requirement in our sample compared to other published research.[23–25] The Edmonton group published data demonstrating a 5-year graft survival rate of around 80%[17] and recent 20-year follow-up demonstrating a Kaplan–Meier estimate of 8% insulin independence at 20 years.[8] We observed a similar cumulative survival rate in the insulin-independent group at 10 years following transplant (Figure 3b). Few centres have significantly longer follow-up available. The insulin independence rates were lower in our sample (30.0%) compared to other published studies,[8,17,26] reflecting the divergence in endpoints between centres. 'Graft survival' has also been expressed in terms of insulin independence duration following transplant, in centres where more significance is placed on insulin independence.[17]

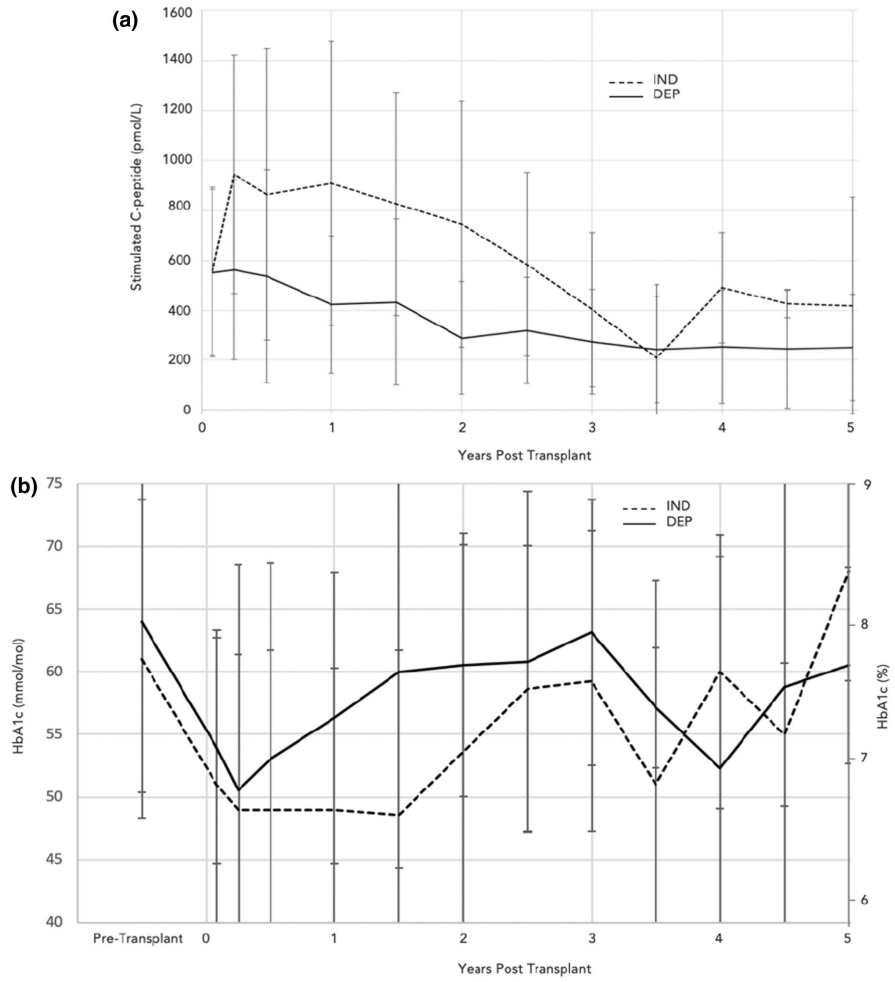

FIGURE 1 90-minute C-peptide (a) and HbA1c (b) over the first 5 years following initial transplant. Error bars indicate the standard deviation (SD).

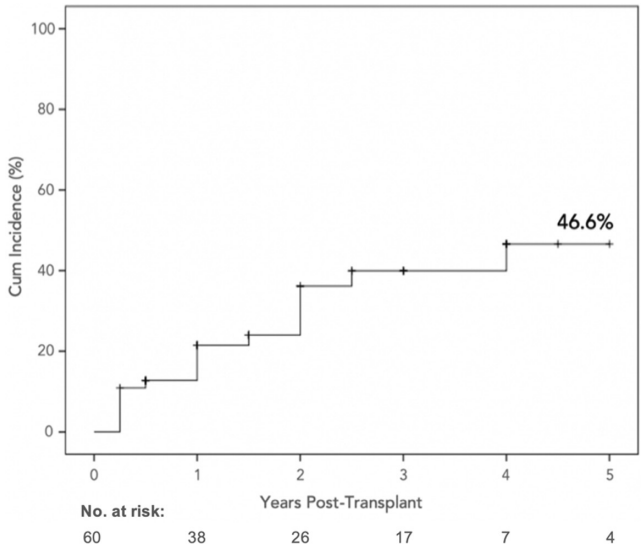

FIGURE 2 Cumulative incidence of severe hypoglycaemia (SH) relapse events. Data were censored for patients without SH relapse at the end of available follow-up.

We did not observe any significant association between infused islet mass and post-transplant insulin requirements. The majority of patients in our sample who received multiple transplants did not achieve insulin independence. Conversely, insulin independence was achieved in five patients following one transplant. Insulin independence following a single islet transplant has also been reported elsewhere in the literature.[27,28] It would be useful to investigate the impact of infused islet mass, number of transplants and time between transplants on post-transplant insulin requirement further, in order to shed light on this.

4.1 | Strengths and limitations

We used outcomes widely recognised in the literature and clinical practice.[17,23,29] The use of quantitative variables provided objective endpoints to evaluate graft function following transplant. We were able to analyse data on all consecutive patients receiving islet transplantation over the investigation period with the exception of one patient who declined follow-up, preventing selection bias or convenience sampling effects.

This is the largest UK single-centre study of islet transplant to date. As such, procedure-related variables

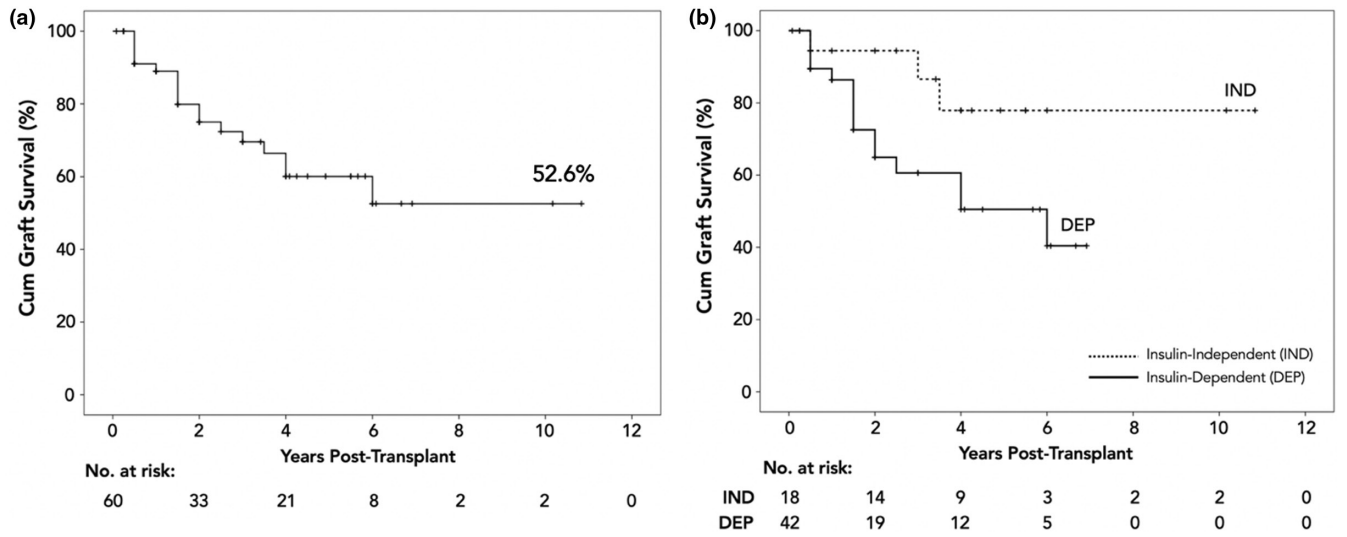

FIGURE 3 Kaplan–Meier curves of graft survival overall (a) and stratified by insulin independence (b). Data were censored for patients with a functional graft at the end of available follow-up.

remained largely constant throughout the data collection period. For example, ward-based pre-operative management, post-operative immunosuppression regimen and supportive care followed the same protocol for each consecutive patient. This helped control for confounders related to the transplantation procedure as well as subsequent management and follow-up. The sample size was relatively small, with only 60 included patients at the end of data collection. There was therefore potentially larger variability in our sample and meaningful statistical analysis was limited.

There were limitations associated with the retrospective analysis design of this study. This increased the risk for information bias or misclassification. However, as our data were collected prospectively over the investigation period, such biases were limited compared to a retrospective data collection design. Given the continuous recruitment of patients throughout the transplant programme, there was variation in available follow-up time between patients, leading to a high volume of censored patients throughout the data collection period, which could have influenced the long-term cumulative graft survival outcomes.

There may have been a confounding effect of the number of islet infusions patients received on metabolic outcomes. However, the intention to treat (to achieve clinically significant graft function) remained constant in our sample. Patients only received a third infusion in the absence of clinically significant graft function. Conversely, if patients achieved clinically significant graft function following one infusion, a second was not indicated. We aimed to compare outcomes between patients who achieved insulin independence following transplantation versus those who did not, irrespective of number of transplants received. Future research would be needed to determine the effects of number of islet infusions on metabolic outcomes and whether this impacts insulin independence.

There were also limitations to the recording of SH events. SH events were quantified for values below 50, or recorded as '>50'. This resulted in a lack of continuous data available for comparison between groups. Furthermore, this was a subjective patient-reported outcome, which may have varied on a case-based level. The American Diabetes Association states that there is not currently a standardised convention for the reporting of SH events in studies.[19] While we did use an accepted definition for severe hypoglycaemia, future research could be improved by more accurately quantifying the incidence of SH events in order to provide continuous data on event frequency.

Despite these limitations, islet transplant remains a novel procedure with only select centres offering the treatment. Due to limited graft availability and strict regulations around patient eligibility, there are few centres with significantly larger sample sizes. We would also hope that the use of the steroid-free immunosuppression regimen pioneered by the Edmonton group (now the gold standard worldwide), improved the generalisability of our results. Indeed, our outcomes reflect those of previous single and multi-centre studies.[8,28-30]

4.2 | Future directions

Other than pre-transplant insulin requirement, we did not find any significant explanatory variables for insulin independence following islet transplant at the univariate level. Given the small sample size, we were not able to conduct any statistically meaningful multivariate analysis

to identify predictors of insulin independence. There are data to suggest that infused islet mass may predict insulin independence following transplant.[28] Future research with larger sample sizes would be useful to identify predictors for insulin independence.

The management of diabetes-related complications represents a significant economic burden around the world.[31-33] Additionally, data suggest the costs attributed to T1DM are disproportionately higher than that of Type 2 Diabetes, accounting for the size of the respective populations.[31] Given the favourable long-term outcomes of islet transplant and globally reduced insulin requirement, a detailed cost-effectiveness analysis would be of interest, particularly as there is very limited published literature on this to date.

Finally, there is an increasing prevalence in the use of extended criteria donors (ECD) for islet transplantation. This has been proposed as an explanation for inferior outcomes of islet transplantation compared to whole organ pancreas transplantation.[34] However, data suggests that outcomes observed using ECDs are comparable to those observed under more conservative practice.[35,36] While the implications of ECD use on insulin independence remain unclear, the use of ECDs could significantly increase the organ pool and allow many more patients to benefit from this treatment, as well as reducing the pressures associated with large transplant waiting lists. Further research into ECD-related outcomes could potentially redefine donor criteria and widen access to islet transplantation around the world.

In conclusion, our findings demonstrate significantly improved graft survival, glycaemic control and metabolic outcomes at 1 year following the initial transplant in patients who achieved insulin independence compared to those who did not. Future studies could evaluate ECD-related outcomes and investigate predictors of insulin independence in more detail, in order to further improve patient outcomes and optimise the future of pancreatic islet transplantation.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest to declare. No funding was received to support this research.

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