Original Article

Assessment of long-term graft function following total pancreatectomy and autologous islet transplantation: the Leicester experience

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Background: Total pancreatectomy and islet autotransplantation (TPIAT) is a recognised treatment for chronic pancreatitis (CP) with the potential to mitigate or prevent pancreatogenic diabetes. We present our 10-year follow-up of TPIAT patients.

Methods: The University Hospitals of Leicester performed 60 TPIAT procedures from September 1994 to May 2011. Seventeen patients completed their 10-year assessment and were grouped using the modified Auto-Igls criteria; good response, n=5 (insulin-independent for first 5 years post-TPIAT); partial response, n=6 (insulin requirements <20 iU/day post-TPIAT) and poor response, n=6 (insulin requirements ≥20 iU/day post-TPIAT). C-peptide, haemoglobin A1c (HbA_{1c}) and oral glucose tolerance test (OGTT) were undertaken preoperatively (baseline), then at 3, 6 months and then yearly for 10 years. Data was analysed using analysis of variance (ANOVA).

Results: Median C-peptide levels were significantly higher, 120 minutes following OGTT, in the "good response" compared to "partial" and "poor" groups (two-way ANOVA test, P<0.0001). All groups demonstrated preservation of C-peptide release. HbA_{1c} levels were significantly lower in the "good response" compared to "partial" and "poor" groups (two-way ANOVA test, P<0.0003 and P<0.0001). Median fasting glucose levels at 30 and 120 min following OGTT, were significantly lower in the "good response" compared to "partial" and "poor" groups (two-way ANOVA test, P<0.0001 and P<0.0001).

Conclusions: TPIAT preserves long-term islet graft functions in 10-year follow up. Even in patients in the poor response group, there is evidence of C-peptide release (>0.5 ng/mL) after OGTT stimulation potentially preventing long-term diabetes-related complications.

Keywords: Islet autotransplantation (IAT); chronic pancreatitis (CP); C-peptide

Submitted Dec 21, 2021. Accepted for publication Apr 13, 2022. Published online Jun 15, 2022.
doi: 10.21037/hbsn-21-558
View this article at: https://dx.doi.org/10.21037/hbsn-21-558

Introduction

Total pancreatectomy (TP) is the preferred treatment option in patients with chronic pancreatitis (CP) and intractable pain when all non-surgical options have been employed and quality of life remains poor. An autologous islet cell transplantation prevents or mitigates the risk of post-procedure diabetes and total pancreatectomy and islet autotransplantation (TPIAT) is currently performed routinely in the United States (1-3), United Kingdom (4), Switzerland (5) and South Korea (6). An increasing number of centers around the world are developing their own TPIAT programs and the results of a recent meta-analysis

confirmed the overall efficacy of islet autotransplantation (IAT) in the short term (7). As a consequence of the multiple reports of the short and long term benefits of IAT multiple insurance companies will now remunerate patients and institutions when the procedure is performed for intractable pain from CP in both non-diabetic patients and C-peptide positive diabetics (8).

Studies of the long-term outcomes following TPIAT have demonstrated significant pain relief and improved quality of life (9) although the proportion of patients who are insulin-independent varies between centres (10). The unpredictable long-term post-TPIAT graft function is likely to be due to numerous, poorly defined factors. A recent meta-analysis by Wu *et al.* suggested that the islet equivalents (IEQ) per kg body weight (IEQ/kg) was significantly associated with the risk of requiring exogenous insulin post-transplant (10). A large series of TPIAT patients from Minnesota also identified alcohol abuse and duration of CP as other factors contributors contributing to graft failure (11). Furthermore there is also evidence that the inflammatory response produced during and immediately following islet cell infusion may also influence graft survival and the long-term loss of function (12). Although it is clear that these factors are important in determining long-term post-pancreatectomy graft function a number of studies have failed to identify a consistent method of assessment following TPIAT. The International Pancreas and Islet Transplant Association (IPITA) and European Pancreas and Islet Transplantation Association (EPITA) held a workshop to develop a consensus statement which could be used to assess the function and failure of current and future forms of β-cell replacement therapy. The Igls criteria, discussed and clarified during the IPITA/EPITA Opinion Leaders Workshop in Igls, Austria 2017 is a method for classifying clinical outcomes following beta cell replacement therapy. They are based on haemoglobin A1c (HbA1c) levels, severe hypoglycaemia episodes (SHE), the reduction in insulin needs from baseline, and increase in C-peptide levels from baseline (13).

Gołębiewska *et al.* also used the modified Igls criteria, adjusted for islet function in TPIAT patients (14) using insulin requirements after TPIAT, HbA1c levels and measurable C-peptide levels. Recently, Minnesota also reported the application of the Auto-Igls criteria in a large cohort of patients (n=379) to evaluate TPIAT outcomes (15). We have a cohort of patients where long-term outcomes can be assessed, and we have assessed this group using these modified Igls criteria (*Tables 1*,*2*).

C-peptide is routinely used for the assessment of islet cell function following transplantation (16) but also has important biological roles. C-peptide augments blood flow in skeletal muscle and skin and improves nerve function in type 1 diabetes where C-peptide is absent (17,18). Myocardia dysfunction and poor perfusion are partially reversed by C-peptide infusion (19), renal function improved with reduced glomerular hyperfiltration and urinary albumin excretion and glucose utilization is increased in type I diabetic patients (20).

To date there are few data regarding the long-term islet graft function after TPIAT. This study presents the long-term outcomes from a series of patients who have undergone continued surveillance for 10 years following TPIAT. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-558/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of University Hospitals of Leicester NHS Trust and informed consent was taken from all individual participants.

Patients

A total of sixty patients underwent TPIAT at our centre from 1994–2011 (*Table 1*). Sixteen patients died in the follow-up period and the responsible clinical problems are shown in *Table 3*. Twenty-nine patients are presently alive for more than ten years post-procedure. Twelve of twenty-nine patients were lost to follow-up. Seventeen patients underwent regular follow-up and assessment of graft function for over ten years (*Figure 1*). These patients were separated into three groups using the modified Auto-Igls classification (15). The cohorts were defined as good response, n=5, (defined as being insulin-independent for first 5 years post TPIAT); partial response, n=6 (exogenous insulin requirements <20 iU/day post TPIAT) and poor response, n=6 (≥20 iU/day post TPIAT) (*Figure 1*, *Tables 2*,*4*).

Islet isolation and transplantation

Islets were prepared and infused as previously described (21). The pancreas was digested with Neutral Protease NB GMP Grade in combination with purified Collagenase

Table 1 Patient demographics and clinical characteristics

Parameter	Patients (n=60)
Age at operation (years)	44±11
Sex, female, n (%)	38 (63.0)
Height (m)	1.7±0.9
Weight (kg)	63±14
BMI	22.7±4.5
Family history of pancreatitis, n (%)	
Yes	2 (3.3)
No	51 (85.0)
Not reported	7 (11.7)
Family history of diabetes, n (%)	
Yes	8 (13.3)
No	42 (70.0)
Not reported	10 (16.7)
Etiology of chronic pancreatitis, n (%)	
Idiopathic	43 (71.7)
Alcohol	11 (18.3)
Gallstones	3 (5.0)
Pancreas divisum	3 (5.0)
Type of pancreatectomy, n (%)	
Total	57 (95.0)
Partial	3 (5.0)
Pancreas weight (g)	68±22
Volume of pancreatic tissue transplanted (mL)	14±8
Total islets count	260,450 [33,500–879,000]
Total IEQ	142,935 [24,332–1,057,488]
IEQ/kg	2,166 [305–20,385]
IEQ/g pancreas	2,349 [249–17,015]
Mean islet volume (mm^3, $\times 10^{-4}$)	4.4 (0.3–27.0)
Total islet volume (mL)	0.25 (0–1.9)
GTT 0 min (mmol/L)	4.9 (3.7–6.7)
GTT 30 min (mmol/L)	7.8 (1.9–14.1)
GTT 120 min (mmol/L)	5.9 (2.5–17.8)
HbA1c	5.5 (4.4–9.7)
C-peptide 0 min (ng/mL)	1.5 (0.2–5.9)
C-peptide 30 min (ng/mL)	4.5 (0.8–13.6)
C-peptide 120 min (ng/mL)	5.6 (1.0–12.5)

Data are presented as mean ± standard deviation or median (range), unless otherwise specified. BMI, body mass index; IEQ, islet equivalent; GTT, glucose tolerant test; HbA1c, haemoglobin A1c.

NB 1 GMP Grade (SERVA Electrophoresis GmbH, Heidelberg, Germany). Unpurified whole pancreatic digest was suspended in M199 transplant media containing 20% human serum albumin. The islets were prepared whilst the surgeons completed the gastrojejunostomy and choledochojejunostomy reconstruction (22). Immediately prior to the islet cell infusion patients received 5,000 units of heparin intravenously. This has always been the policy in Leicester rather than heparin being included with the islets during the infusion (or 50% systemic and 50% with the islets in some units). The rational for the systemic heparinisation immediately prior to the islet cell infusion is to ensure that anticoagulation is adequate from the beginning of the infusion which is not possible in the early stages when heparin is included with the infusion. The islets were infused into the portal vein via the middle colic vein or umbilical vein (after 1998) over 20–30 minutes (23). During the islet cell infusion portal vein pressures were continuously monitored to ensure they did not exceed 20 mmHg.

The islet yield was converted into IEQ, with the diameter standardised to 150 μm. Islet viability in the final product was evaluated with fluorescein diacetate/propidium iodide staining.

Data collection and assessment of islet graft function

Before surgery, fasting blood samples were drawn for the assessment of glycosylated haemoglobin (HbA1c). Patients underwent an oral glucose tolerance test (OGTT), and samples were collected for plasma glucose and serum C-peptide levels at 0, 30 and 120 min (baseline levels). Islet function was assessed with C-peptide, enzyme-linked immunosorbent assay (ELISA) (ELISA DRG Diagnostics, Nottingham, UK). Follow-up assessment of

Table 2 Modified Igls classification after islet auto-transplantation

Classification	HbA1c	SHE (per year)	Insulin dose	C-peptide
(A) Igls				
Optimal	<6.5%	None	None	> Baseline
Good	<7%	None	<50% Baseline	> Baseline
Marginal	Baseline	< Baseline	≥50% Baseline	> Baseline
Failed	Baseline	Baseline	Baseline	Baseline
(B) Minnesota Auto-Igls				*
Optimal	<6.5%	None	None	>0.5 ng/mL (≥0.2 ng/mL)
Good	<7%	None	<0.5 units/kg/day	>0.5 ng/mL (≥0.2 ng/mL)
Marginal	≥7%	≥1	≥0.5 units/kg/day	>0.5 ng/mL (≥0.2 ng/mL)
Failed	–	–	–	≤0.5 ng/mL (≥0.2 ng/mL)
(C) Leicester Auto-Igls				*
Good	–	–	None (up to 5 years)	>0.5 ng/mL (≥0.2 ng/mL)
Partial	–	–	<20 units/day	>0.5 ng/mL (≥0.2 ng/mL)
Poor	–	–	20–40 units/day (within 5 years)	>0.5 ng/mL (≥0.2 ng/mL)
Failed	–	–	–	≤0.5 ng/mL

*, C-peptide stimulated (fasting). (A) Original Igls classification; (B) Minnesota Modified Auto-Igls classification; (C) Leicester Modified Auto-Igls classification. HbA1c, haemoglobin A1c; SHE, severe hypoglycaemia episodes.

islet graft function was made at 3, 6 and 12 months, post-transplantation and annually thereafter for at least ten years.

Statistical analysis

All data was entered into an Excel database (Microsoft, Redmond, Washington, USA) and analysis performed using GraphPad Prism for Windows, version 6.02 (GraphPad Software, Inc., California, USA). Descriptive statistics consisted of the mean and standard deviation for parametric distributions. Comparison amongst groups and over time were performed with the analysis of variance (ANOVA) test for repeated measures for parametric variables. P values <0.05 were considered statistically significant.

Results

Patients

Between September 1994 and May 2011, sixty transplants underwent TPIAT in Leicester. Patient demographics and clinical characteristics are presented in *Table 1*. Long-term islet graft function was assessed after exclusion of the 16 patients who had died in the follow-up period. No patient died from complications related to their surgery and the causes are shown in *Table 3*. Age, body mass index (BMI) and the aetiology of pancreatitis were not significantly different in these groups (*Table 4*). Transplanted IEQ/kg did vary between groups but due to the small sample size no meaningful conclusions can extracted from these data (*Table 4*).

Insulin requirement after TPIAT

Table S1A-S1C and *Figure 2A* show the three subgroups according to insulin requirements following TPIAT. In the "good response" group, all patients were insulin-free for first five years and required minimum support subsequently (<10 units/day up to 10 years post TPIAT). Insulin requirements were below 20 units/day in the "partial response" group and more than 20 units/day in the "poor response" group post TPIAT (Table S1A-S1C and *Figure 2A*).

Table 3 Length of follow up and cause of death in patients following TPIAT

No	Cause of death	Islet length of f/u
1	Alcohol	4 years
2	Heart disease	No f/u
3	Unknown	6 months
4	Unknown	2 years
5	Alcohol	1 years
6	Unknown	6 months
7	Unrelated to surgery	7 years
8	Unknown	3 years
9	Natural causes	6 years
10	Unknown	No details as in witness protection
11	Alcohol	7 years
12	Alcohol	1 years
13	Diabetes complications	6 years
14	Alcohol	10 years
15	Unknown	8 years
16	Unknown	16 years

TPIAT, total pancreatectomy and islet autotransplantation; f/u, follow-up.

Clinical outcome of diabetes after TPIAT

The baseline HbA1c level preoperatively was below 7% in all groups. Post-operatively, the "good response" group maintained stable levels for up to ten years (*Figure 2B* and Table S1A). HbA1c levels were significantly higher in the "partial" and "poor response" groups compared with the "good response" group (two-way ANOVA P<0.0003 and P<0.0001 respectively), but there was no significant difference between the "partial response" (HbA1c 5.4–8.7%) and "poor response" groups (HbA1c 7.1–9.0%) in respect of exogenous insulin supplementation (*Figure 2B* and Table S1B,S1C).

The "good response" group demonstrated better glucose control following OGTT (*Figure 3A* and Table S1A). Glucose levels were elevated significantly in both partial and "poor response" groups compared with the "good response" group at both 30 min and two hours after OGTT (two-way ANOVA P<0.0001 and P<0.0001 respectively). In comparison between the "poor response" and "partial response" groups, there was no significant different in glucose levels at 30 and 120 min after OGTT (*Figure 3B,3C* and Table S1A-S1C).

Islet graft function following TPIAT

All patients in the series remained C-peptide positive. Patients in the "good response" group, demonstrated C-peptide levels which increased significantly 30 minutes following an OGTT (two-way ANOVA test, P=0.0006) with a further increase by 120 min (two-way ANOVA, P<0.0001). C-peptide levels were also significantly raised in the "partial response" group at 30 and 120 min compared to baseline levels (two-way ANOVA test, P=0.0066 and P<0.0001). A flattened increase in the elevation of C-peptide levels was noted in the "poor response" group with no elevation by 30 minutes but a significantly increased level by 120 min compared with baseline levels (two-way ANOVA, P=0.0032) (*Figure 4* and Table S1A-S1C).

Between groups, mean C-peptide levels were significantly higher in the "good response" compared to the partial and "poor response" subgroups at baseline (two-way ANOVA, P=0.0013 and P=0.0063 respectively), at 30 min (two-way ANOVA test, P=0.0009 and P=0.0003 respectively) and at 120 min (two-way ANOVA, P<0.0001 and P<0.0001 respectively).

Discussion

TP is a recognised treatment for patients with intractable pain from CP when all non-surgical options have been employed and quality of life remains poor (24). Without a post-procedure islet autotransplant patients may experience poorly controlled, labile "brittle" diabetes (25). IAT has the potential to confer insulin independence in a proportion of patients and preserve a degree of islet endocrine function in all patients. TPIAT significantly lowers the insulin requirements when compared with TP alone and HbA1c levels are showing trend of lower in patients following TPIAT compared with TP alone (24). Patient survival may also be improved with TPIAT compared to TP alone although this is likely to be due to myriad factors including improved glucose control/insulin independence, the duration of symptoms prior to surgery, the aetiology of the CP, continuation of precipitating factors and domestic and cultural circumstances (9). TPIAT is a safe procedure, with no associated mortality to surgery (*Table 3*). Fazlalizadeh

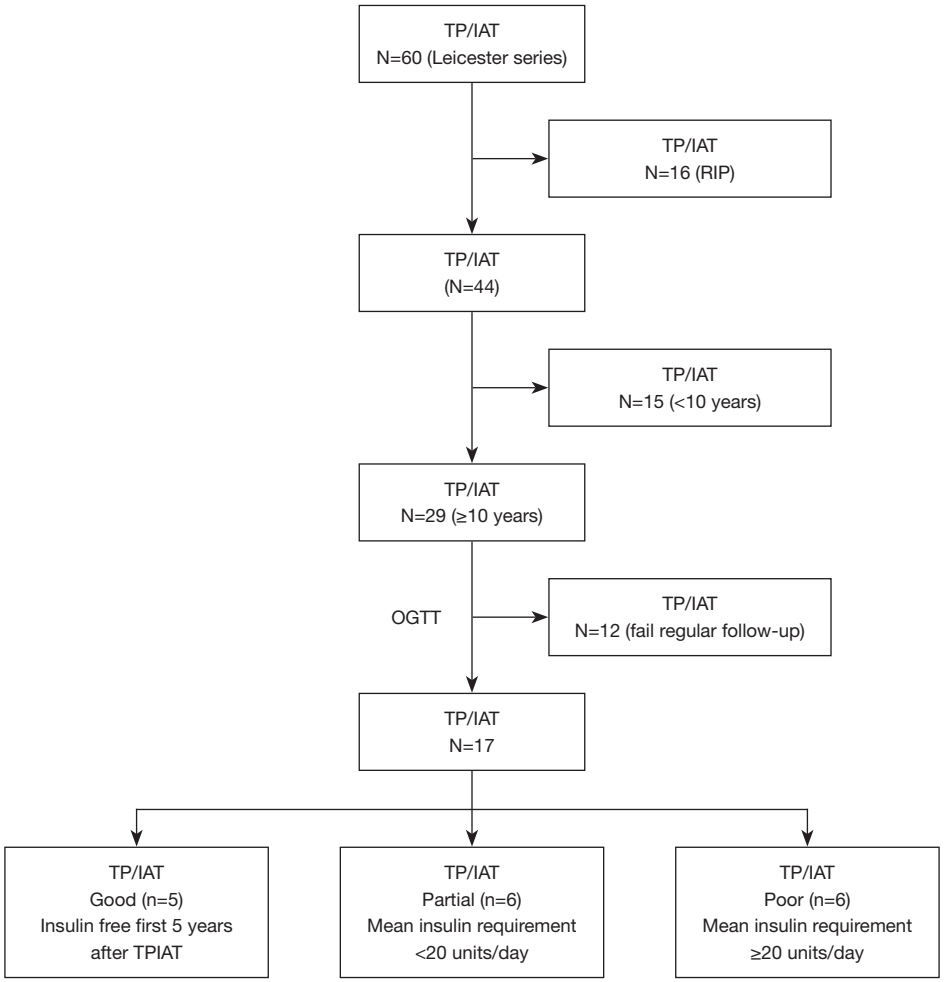

Figure 1 Method of patient selection for assessment. TP, total pancreatectomy; IAT, islet autotransplantation; RIP, rest in peace; OGTT, oral glucose tolerant test; TPIAT, total pancreatectomy and islet autotransplantation.

Table 4 Clinical characteristics and islet isolation data following islet auto-transplantation

Parameter	Good (n=5)	Partial (n=6)	Poor (n=6)
Age, years	26–53	35–61	28–55
BMI (kg/m^2)	20.45–29.86	17.31–20.66	15.21–32.46
Aetiology of pancreatitis	Alcohol (n=2); non-alcohol (n=3)	Idiopathic (n=5); congenital (n=1)	Idiopathic (n=3); small duct (n=1); pancreas divisum (n=1); polycystic (n=1)
Pancreas weight (g)	19.4–104	52–98	22.75–93.25
Total IEQ, mean [range]	94,455 [24,687–218,920]	105,832 [44,116–192,850]	128,826 [37,119–220,000]
IEQ/kg, mean [range]	1,345 [319.5–2,764.14]	1,994 [882.3–3,506.36]	2,020 [614.55–4,230]
% cleavage	12–77%	25–87%	20–68%
Islet volume (mm^3, $\times 10^{-4}$)	3.828–11.213	2.616–14.349	6.247–44.320

BMI, body mass index; IEQ, islet equivalent.

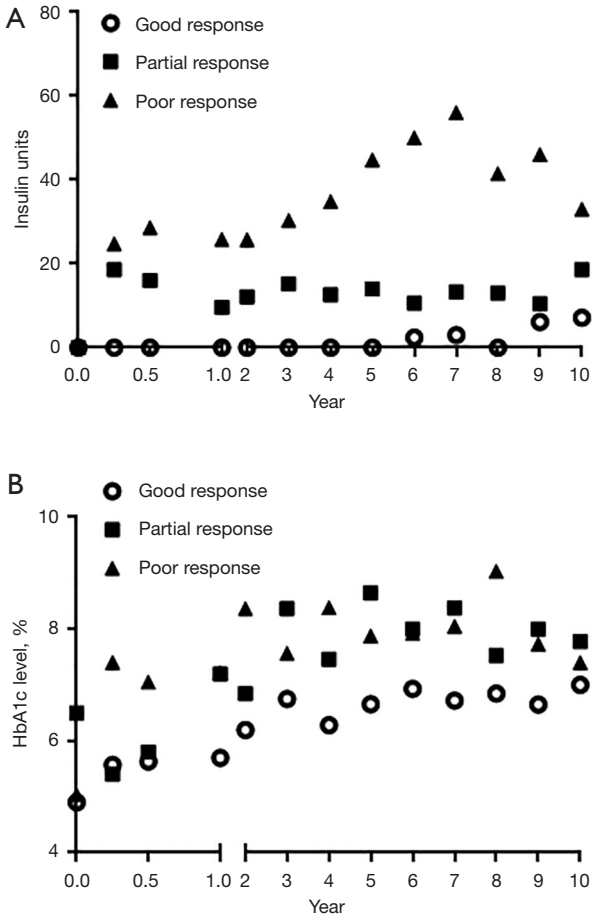

Figure 2 Insulin requirement and Hb1Ac following TPIAT. (A) Mean insulin requirement at pre-operatively, at 3, 6 and 12 months post-procedure and annually up to 10 years. (B) Mean HbA1c level at pre-operatively at 3, 6 and 12 months post-procedure and annually up to 10 years. HbA1c, haemoglobin A1c; TPIAT, total pancreatectomy and islet autotransplantation.

et al. reviewed the Nationwide Inpatient Database in United States between 2002–2012 which showed no mortality (26).

Long-term data following TPIAT has already been published from our group in 2008 (4) and Robertson *et al.* reported that a small number of patients demonstrated stable β-cell function and normal glucose level up to 13 years following TPIAT (27). Contrasting with the results from our series and those of Robertson, Wahoff *et al.* found that 34% of patients were insulin independent at 2 years but only one patient at 10 years post-transplant (28).

We used the Minnesota group's modified Auto-Igls

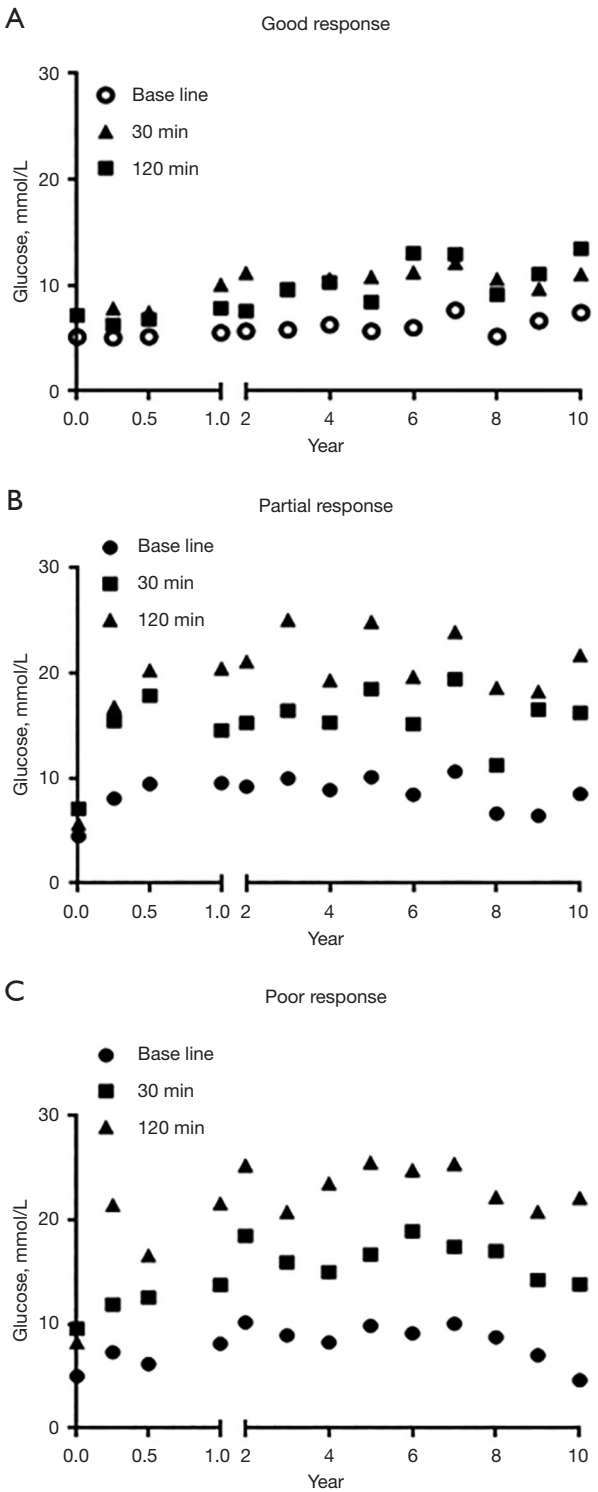

Figure 3 Mean glucose level at baseline, 30 and 120 min after an OGTT in good response (A), partial response (B) and poor response (C) groups. OGTT, oral glucose tolerant test.

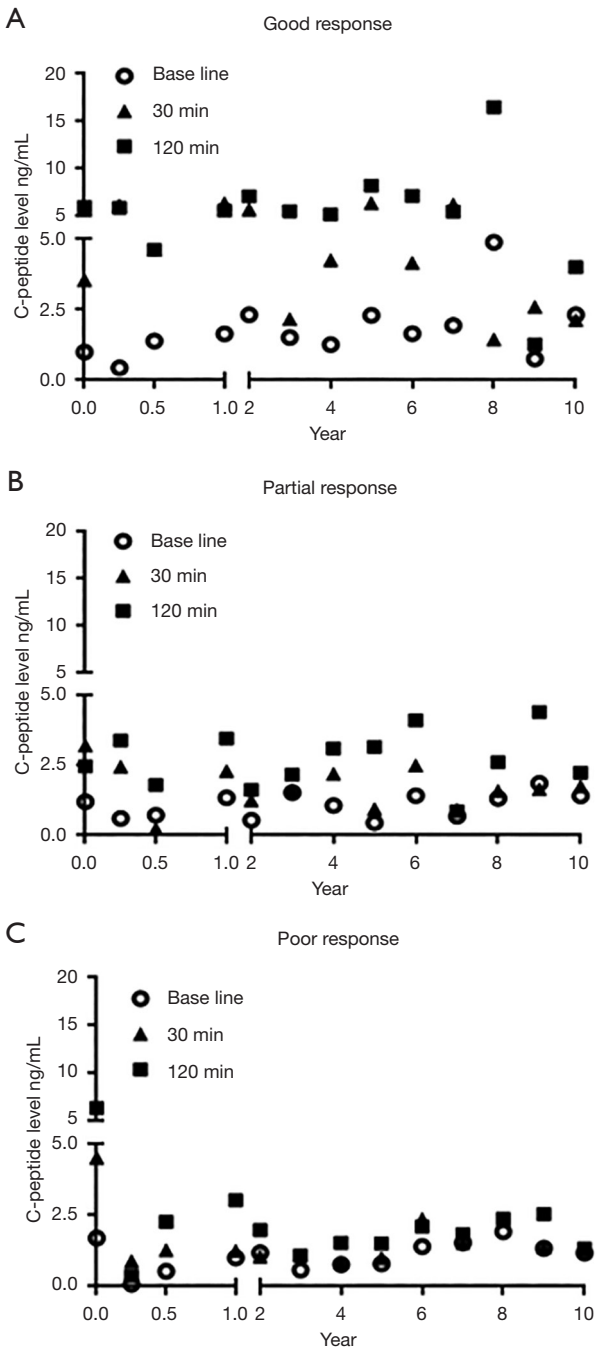

Figure 4 Mean C-peptide level at baseline, 30 and 120 min after an OGTT in good response (A), partial response (B) and poor response (C) groups. OGTT, oral glucose tolerant test.

criteria for to classify patients as "good", "partial" or "poor" responders corresponding to those reported and classified by the Minnesota group as "optimal", "good" and "marginal" where optimal was defined as an HbA1c ≤6.5%, good as an HbA1c <7% and marginal if the HbA1c ≥7% (15). "Optimal" responders required no insulin, "good" responders required <0.5 unit/kg/day; and marginal responders required ≥0.5 unit/kg/day.

In our "good response" group, 29.4% (5/17) had been insulin free for 5 years and 17.6% (3/17) remained insulin free for more than 10 years. In the "partial response" group, two patients had a period of insulin-independence for 6 months after TPIAT. In this series, 41.4% (12/29) of the patients did not attend the clinic after surgery or stopped follow-up after few years (*Figure 1*). Relevant factors influencing attendance at follow-up included lifestyle, distance from the tertiary hospital, moving away from the area and the onset of medical conditions inhibiting travel. Some centres unable to obtain blood for C-peptide measurements used daily insulin requirements as a surrogate marker of graft function (11).

Whilst previous studies have demonstrated a strong link between islet yield and islet graft function (29,30) in our series islet yield did not correlate with long-term function although the size of the cohort available for assessment is likely to be responsible. Two patients were insulin-independent for more than ten years following TPIAT with low islet yields (<1,000 IEQ/kg). In one patient in our series, we postulated that the small size of islets transplanted had prevented central necrosis and potentially improved long-term graft function (31). A number of additional factors are believed to effect islet graft viability including alcohol as the aetiological factor of the induced CP and the duration of pancreatitis (11).

"Brittle diabetes" following TP is avoided when IAT is possible and appropriate. In our series, C-peptide levels remained remarkably stable for more than 10 years in the "good response" group. For patients in the "partial response" group, C-peptide levels rose significantly following glucose stimulation confirming that a degree of islet function was preserved. Even in the "poor response" group by 120 minutes C-peptide levels rose following stimulation. Islet cell graft failure as defined by the International Islet Transplant Registry as C-peptide levels below 0.3 ng/mL (32). These results demonstrate that TPIAT with an adequate islet cell mass can prevents graft failure and ensure a clinically significant level of graft function (mean C-peptide levels more than 0.3 ng/mL) in all patients.

Conclusions

TPIAT relieves the pain from CP, preserves endocrine

function and mitigates the risk of poorly controlled diabetes. These data demonstrate that endogenous insulin production is preserved and can be demonstrated for at least 10 years following TPIAT. Further long-term follow-up is required in larger series of patients to confirm these very encouraging results and enable the identification of the factors which may influence long-term graft function.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-558/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-558/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-558/coif). ARD serves as the unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of University Hospitals of Leicester NHS Trust and informed consent was taken from all individual participants.

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Cite this article as: Pollard CA, Chung WY, Garcea G, Dennison AR. Assessment of long-term graft function following total pancreatectomy and autologous islet transplantation: the Leicester experience. HepatoBiliary Surg Nutr 2023;12(5):682-691. doi: 10.21037/hbsn-21-558

Supplementary

Table S1 Metabolic outcomes in good response (A), partial response (B) and poor response (C)

(A) Good response

Year	Pre op	3/12	6/12	1	2	3	4	5	6	7	8	9	10
Good response (n = 5)													
Insulin (U/d)	0	0	0	0	0	0	0	0	2.4±5.4	3±6.7	0	6.2±13.9	7.2±16.1
HbA1c %	4.9±0.4	5.6±0.4	5.6±0.6	5.7±0.3	6.2±0.8	6.8±1.3	6.3±1.3	6.7±1.4	6.9±0.9	6.7±1.7	6.9±0.9	6.7±0.9	7.0±1.1
Stimulated C-peptide (ng/mL), mean ± SD													
0 min	1.0±0.4	0.4±0.6	1.4±1.8	1.6±1.5	2.3±2.0	1.5±0.6	1.3±0.35	2.3±0.7	1.7±0.9	1.9±1.3	4.9±0.0	0.8±0.1	2.3±1.3
30 min	3.5±3.4	6.1±4.8	4.6±5.4	6.3±5.6	5.6±2.6	2.2±1.0	4.2±3.4	6.3±2.6	4.1±2.8	6.2±6.1	1.4±0.0	2.6±2.4	2.1±0.9
120 min	5.9±2.7	5.8±5.1	4.6±3.6	5.5±3.8	7.1±3.8	5.5±2.7	5.1±0.9	8.2±4.7	7.1±6.2	5.4±4.8	16.5±0.0	1.3±0.3	4.0±2.8
OGTT (glucose level mmol/L), mean ± SD													
0 min	5.1±0.3	5.1±0.2	5.2±1.0	5.5±0.8	5.7±1.2	5.8±1.8	6.3±1.6	5.7±1.5	6.0±1.6	7.6±3.3	5.2±0.0	6.7±1.9	7.5±3.0
30 min	7.3±1.0	7.8±1.1	7.5±1.8	10.1±1.8	11.2±1.6	9.6±3.1	10.6±2.8	10.8±3.4	11.2±4.9	12.2±6.9	10.6±0.0	9.7±1.4	11.1±5.9
120 min	7.2±0.7	6.3±0.7	6.8±2.1	7.9±3.3	7.6±2.9	9.7±2.0	10.3±4.3	8.4±4.0	13.0±3.4	13.0±7.3	9.1±0.0	11.1±2.2	13.5±5.0

(B) Partial response

Year	Pre op	3/12	6/12	1	2	3	4	5	6	7	8	9	10
Partial response (n = 6)													
Insulin (U/d)	0	18.6±16.8	16.0±13.1	9.6±6.3	12.2±4.9	15.3±5.0	12.6±5.7	14.0±5.4	10.6±3.0	13.3±11.4	13.0±5.3	10.5±2.1	18.7±7.2
HbA1c %	6.5±2.8	5.4±0.0	5.8±1.7	7.2±2.0	6.9±1.0	8.4±1.6	7.5±1.3	8.7±1.8	8.0±1.0	8.4±1.5	7.5±1.1	8.0±1.1	7.8±0.9
Stimulated C-peptide (ng/mL), mean ± SD													
0 min	1.2±1.0	0.6±0.0	0.7±0.3	1.4±0.8	0.6±0.1	1.5±1.2	1.1±0.4	0.5±0.1	1.4±1.7	0.7±0.5	1.3±0.5	1.9±1.2	1.4±0.3
30 min	3.2±0.5	2.5±0.0	0.2±0.4	2.3±1.3	1.3±0.6	1.6±1.0	2.2±1.2	1.0±0.2	2.5±2.8	0.9±0.2	1.6±0.6	1.7±0.0	1.8±1.3
120 min	2.5±0.1	3.4±0.0	1.8±1.2	3.5±2.5	1.6±1.3	2.2±0.6	3.1±1.8	3.2±2.1	4.1±4.3	0.9±0.3	2.6±1.0	4.4±3.9	2.2±1.3
OGTT (glucose level mmol/L), mean ± SD													
0 min	4.5±0.5	8.1±0.1	9.5±5.1	9.5±5.5	9.2±3.7	10.0±3.0	8.9±3.3	10.1±1.8	8.4±4.2	10.6±4.4	6.7±2.5	6.5±1.1	8.5±2.5
30 min	7.1±1.0	15.5±2.5	17.9±4.7	14.6±6.9	15.3±5.0	16.4±5.0	15.3±5.5	18.5±5.8	15.2±7.4	19.4±6.1	11.2±3.0	16.6±6.6	16.2±4.5
120 min	5.7±2.4	16.8±3.4	20.3±10.5	20.5±11.9	21.1±10.8	25.1±8.5	19.3±7.9	24.9±5.8	16.7±9.9	23.9±12.7	18.6±5.5	18.3±9.8	21.7±5.3

(C) Poor response

Year	Pre op	3/12	6/12	1	2	3	4	5	6	7	8	9	10
Poor response (n = 6)													
Insulin (U/d)	0	24.8±11.2	28.6±20.7	25.8±16.4	25.8±14.5	30.3±11.7	34.8±8.1	44.8±11.0	50.0±23.3	56.0±29.4	41.5±0.7	46.0±2.8	33.0±6.1
HbA1c %	5.0±0.6	7.4±0.6	7.1±0.6	7.2±0.6	8.4±0.8	7.6±1.1	8.4±1.3	7.9±1.9	7.9±2.3	8.1±1.3	9.0±1.2	7.7±0.4	7.4±0.0
Stimulated C-peptide (ng/mL), mean ± SD													
0 min	1.7±1.0	0.1±0.1	0.5±0.9	1.0±1.0	1.6±0.6	0.6±0.4	0.8±1.0	0.8±0.7	1.4±1.0	1.5±2.2	1.9±2.7	1.3±0.9	1.2±0.1
30 min	4.5±3.4	0.9±0.8	1.3±2.1	1.3±1.3	1.1±0.8	1.1±0.9	0.8±1.0	1.0±0.8	2.4±2.6	1.5±2.1	2.4±3.1	1.4±1.1	1.3±0.3
120 min	6.3±2.2	0.4±0.2	2.3±2.4	3.0±3.1	2.0±0.7	1.1±1.6	1.5±1.8	1.5±0.9	2.1±1.9	1.8±2.4	2.4±2.8	2.5±1.8	1.3±0.2
OGTT (glucose level mmol/L), mean ± SD													
0 min	5.0±0.4	7.3±4.7	6.2±3.1	8.2±3.0	10.2±1.8	8.9±3.5	8.3±4.2	9.9±4.4	9.1±2.5	10.1±3.5	8.8±3.8	7.0±2.7	4.7±0.8
30 min	9.6±2.6	11.9±6.8	12.6±3.7	13.8±4.6	18.5±1.9	16.0±6.0	15.0±3.7	16.7±1.8	19.0±5.2	17.4±3.6	17.1±0.2	14.3±5.3	13.9±0.2
120 min	8.3±4.6	21.5±0.6	16.6±6.0	21.6±9.0	25.3±2.0	20.8±7.5	23.5±2.9	25.5±2.2	24.8±2.0	25.4±6.8	22.2±2.0	20.8±4.0	22.2±4.2

https://dx.doi.org/10.21037/hbsn-21-558