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ORIGINAL ARTICLE

Pain resolution and glucose control in pediatric patients with chronic pancreatitis after total pancreatectomy with islet auto-transplantation

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Abstract

Background Chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP) in pediatric patients are strongly associated with genetic mutations and lead to pan-parenchymal disease refractory to medical and endoscopic treatment. Our aim was to assess pain resolution and glucose control in patients with CP and ARP following total pancreatectomy with islet auto-transplantation (TPIAT).

Methods We retrospectively analyzed prospectively collected clinical data of 12 children who developed CP and ARP and underwent TPIAT when 21 years old or younger at the University of Chicago between December 2009 and June 2020. Patients with recurrent or persistent abdominal pain attributed to acute or chronic pancreatic inflammation and a history of medical interventions attempted for the relief of pancreatic pain were selected by a multi-disciplinary team for TPIAT. We followed patients post-operatively and reported data for pre-TPIAT, post-operative day 75, and yearly post-TPIAT.

Results All 12 patients experienced complete resolution of pancreatic pain. The overall insulin-independence rate after 1 year was 66% (8/12) and 50% (3/6) at 4 years. Shorter duration of CP/ARP pre-TPIAT, higher mass of islets infused, and lower BMI, BMI percentile, and BSA were associated with insulin-independence post-TPIAT.

Conclusions TPIAT is a viable treatment option for pediatric patients with CP and ARP. Pediatric patients undergoing TPIAT for CP achieved resolution of pancreatic-type pain and reduced opioid requirements. The majority were able to achieve insulin-independence which was associated with lower pre-TPIAT BMI and higher islet mass transplanted (i.e., over 2000 IEQ/kg), the latter of which can be achieved by earlier TPIAT.

Level of evidence Treatment study, Level IV.

Keywords TPIAT · Pain · Opioids · Glucose control · Quality of life

Abbreviations

ARP	Recurrent acute pancreatitis
CFTR	Cystic fibrosis transmembrane conductance regulator
CP	Chronic pancreatitis
DIR	Daily insulin requirement

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ERCP	Endoscopic retrograde cholangiopancreatography
GMP	Good manufacture practice
HbA1c	Hemoglobin A1c
IEQ	Islet equivalent dose
PRSS1	Protease serine 1
PV	Portal vein
QoL	Quality of life
SPINK1	Serine protease inhibitor Kazal type 1
TIPS	Transjugular intrahepatic portocaval shunt
TPIAT	Total pancreatectomy with islet auto-transplantation

Introduction

In the pediatric population, chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP) are strongly associated with genetic mutations [1, 2], and they often lead to progressive severe abdominal pain, opioid-dependence, diabetes, malnutrition, and frequent and prolonged hospitalizations, compromising adequate natural development of children and young adults [3].

Total pancreatectomy with islet auto-transplantation (TPIAT) is a definitive therapeutic option to resolve pain and yet is rarely offered to pediatric patients due to concerns of post-surgical complications and diabetes. Herein, we report our center's 10 year experience with TPIAT in children and young adults and our outcomes for pain resolution and glycemic control.

Materials and methods

Study design

We prospectively collected clinical data from pediatric patients who were referred with symptomatic CP or ARP as children and subsequently underwent TPIAT by the age of 21 at the University of Chicago between December 2009 and June 2020. The study was approved by the University of Chicago Institutional Review Board. Informed consent was obtained from all participating individuals and their legal guardians.

Patient pre-surgical assessment

Patients were assessed and treated by a diverse pediatric multi-disciplinary team including a transplant surgeon. The diagnoses of chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP) were made according to the criteria recommended by the *International Study Group of Pediatric Pancreatitis: In search for a cure (INSPPIRE) consortium* [4], which included two mandatory criteria: (1) a documented history of recurrent episodes of severe abdominal and/or back pain with an elevated serum amylase and/or lipase of at least three times the upper limit of the reference range, and (2) a history of medical interventions for the attempted relief of pancreatic pain.

Debilitating pain and symptoms which significantly compromised activities of daily living including frequent emergency department visits or hospitalizations, impaired psychosocial or emotional well-being, limited physical activity, or a substantial number of days missed at school were indications for surgical referral. Other factors taken into consideration for surgical evaluation included the need for enteral or parenteral feeding, presence of specific mutations and a family history of pancreatitis [2]. Pre-diabetes or diabetes was not considered a contraindication for TPIAT as long as a serum fasting c-peptide was detected. The pediatric patients and their parents and guardians were intimately involved in the entire process and played an active role in the decision to proceed with surgery.

Peri-operative management

In addition to age appropriate vaccines, all patients received a series of specific vaccinations to optimize immunity in case of splenectomy during the TPIAT procedure. Prophylactic antibiotics were administered pre-operatively and discontinued after 24 h. Antibiotic prophylaxis was extended for a total of 7 days in five patients (42%) who had positive bacteriological culture of their final islet product [5].

Total pancreatectomy

All total pancreatectomies included the excision of the duodenum. If possible, the spleen was preserved via the Warshaw technique [6, 7]. Continuity of the gastrointestinal tract was re-established via a hepaticojejunostomy and a gastro- or duodeno-jejunostomy with a pylorus-preserving approach whenever possible. Patients remained intubated in the operating room with an open abdomen until islets were isolated and infused intraportally.

Pancreas processing and islet isolation

The excised pancreas was preserved with cold preservation solution and transported on ice to the nearby University of Chicago GMP facility for further processing. Islets were isolated using the Ricordi method utilizing Liberase (Roche Diagnostics GmbH, Manheim, Germany) for pancreas digestion [6]. Islet purification was performed when pellet tissue volume was above 20 mL [6]. Gram staining and bacterial culture were performed to identify bacterial contamination. The final islet preparation was suspended in transplant media

solution (CMRL 1066, Mediatech Cellgro, Manassas, VA, USA) with heparin added at 70 units per kg of patient body weight.

Islet auto-transplantation

The portal vein was cannulated under direct vision and islets were infused under gravity over 20–30 min. Portal pressure was monitored, and the infusion aborted if the pressure remained persistently above 25–30 mmHg. In two (17%) cases, the remaining islet tissue was injected into spaces within the root of the small bowel and transverse colon mesentery. After the islet infusion, the abdominal incision was closed, and the patients were extubated and transferred to the intensive-care unit (ICU). Prophylactic doses of heparin were continued for 2 weeks post-operatively as detailed in Table 1B. Feeding tubes were not routinely placed. Post-operative pain management is listed in Table 1C. Intravenous opioids were transitioned to oral medications as soon as possible.

Pain assessment

After discharge patients were gradually weaned off opioids and transitioned to alternative regimens under the guidance of pain management specialists. Pain was assessed based on the use of opioids pre-operatively, on post-operative day (POD) 75, and at scheduled annual follow-up visits. Opioid dose requirements were converted to a standardized morphine equivalent dose (MED) using an online tool to facilitate comparison [8].

Glycemic control

Continuous exogenous insulin supplementation was started intravenously immediately after the pancreas excision and transitioned to insulin injections once oral intake was resumed. Intensive insulin support was continued for at least 2–3 months and until insulin requirements were minimal with optimal glucose control corresponding to the criteria for insulin-independence.

The evaluation of glycemic control was based on measurements of serum glucose levels, fasting c-peptide, HbA1c, and the required daily dose of insulin, which allowed for the calculation of Islet graft function based on the BETA-2 score [9, 10]. Patients' blood glucose and insulin diaries were reviewed regularly as well. Insulin independence was defined as adequate glycemic control without exogenous insulin treatment for 14 or more consecutive days. Adequate glycemic control was defined as fasting glucose < 126 mg/dL more than 3 times per week, HbA1c < 6.5%, and 2 h postprandial glucose not exceeding 180 mg/dL more than 4 times per week.

Statistical analysis

Descriptive statistics are expressed as a median with an interquartile range (IQR) and minimum–maximum range. Univariate comparisons were performed using Mann–Whitney *U* test and Fisher test. The impact of covariates was tested using Spearman correlation, logistic regression and mixed linear models. Standardized β-coefficients were reported as strengths of association between variables and continuous outcomes, while odds ratios with 95% Confidence Intervals were used for dichotomous outcomes. Due to the small number of patients, the likelihood ratio test (LR-test) was used to allow for the selection of explanatory clinical variables with the highest influence on multivariate logistic regression. Spearman correlation was used to test the relationship between continuous variables. A p value of < 0.05 was considered statistically significant. No correction for multiple hypothesis testing was applied. The statistical analysis was performed using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA) and Python 3.8.

3. Results

Demographics, surgical procedure, and post-operative course

Seven males (58%) and five females (42%) with a median age of 16 (13.8–19) and a median BMI percentile of 75 (50–84) were included in the study. Baseline characteristics of the patient group are presented in Table 1A, characteristics of the TPIAT procedure in Table 1B, and post-operative course in Table 1C. The median period of follow-up was 36 months (12–48).

Pain

Prior to surgery, all 12 patients reported pancreatic pain localized in the upper abdomen with or without radiation to the back. All required oral opioid administration prior to TPIAT: seven (58%) daily, and the remaining five (42%) were on opioids intermittently.

After TPIAT, all 12 patients experienced complete resolution of pancreatic pain. Fewer patients required opioids at each scheduled post-operative follow-up time point. This difference was statistically significant compared to the pre-operative opioid requirement (Fisher, all $p < 0.005$, Fig. 1A, B). Daily opioid requirements decreased post-operatively from 13 mg/day (0–30) of Morphine Equivalent Doses (MED) to 0 (0–5) on day 75 and to 0 (0–0) at 1 year. Opioid requirement was negatively associated with the time from the TPIAT procedure (mixed model $\beta = -0.6073$, $p = 0.0001$), and positively associated with age at the time of surgery

Table 1 Data related to (A) patient demographics and (B) TPIAT procedure

	Median (IQR) [min–max] *N* (%)
A. Demographics	
Chronic pancreatitis with constant pain (CP) (N)	4 (33%)
Acute recurrent pancreatitis (ARP) (*N*)	8 (66%)
Age at diagnosis, years	11 (2.8–15) [0.8–17]
Age at TPIAT, years	16 (13.8–19) [9–21]
≤18 years old	8 (66%)
>18 years old	4 (33%)
Sex	
Male	7 (58%)
Female	5 (42%)
BMI at TPIAT, kg/m^2	21.1 (18.7–23.3) [17.5–33]
BMI at TPIAT, percentile	75 (50–84) [5–98]
BSA at TPIAT	1.7 (1.5–1.8) [1.1–2.1]
Prealbumin	18 (12–20) [8–24]
Duration of pancreatitis since diagnosis, years	5.5 (2.8- 8.9) [1–19]
Etiology	
Genetic mutation (PRSS1 and/or CFTR)	10 (84%)
Autoimmune	1 (8%)
Idiopathic[a]	1 (8%)
Number of prior	
ERCP/stent	2 (0- 3) [0- 4]
Pancreatic surgeries	0
Number of acute pancreatitis episodes during previous 12 months	6 (5–6)
	[2–12]
Number of previous hospital ED visits/admissions prior to TPIAT	13 (4.8- 33.5) [3–100]
Pre-TPIAT, number of patients required:	
Total parenteral nutrition	1 (8%)
Tube feeding	2 (16%)
No TPN/ no tube feeds	9 (75%)
Post-TPIAT, number of patients required:	
Total parenteral nutrition	4 (33%)
Tube feeding	0
No TPN/ no tube feeds	8 (66%)
Pre-TPIAT daily opioid use in morphine equivalent dose (MED)	23 (0–37) [0–84]
Insulin requirement prior to surgery	1 (8%)
HbA1c < 5.7%	9 (75%)
5.7% < HbA1c < 6.5%	3 (25%)
HbA1c > 6.5%	0
B.TPIAT procedure	
Total duration of procedure (incision to skin closure),	9 h 6 min (8 h 48 min–9 h 52 min) [8 h 11 min–11 h 5 min]
Islet mass transplanted—islet equivalent (IEQ),	193,152 (95,040–221,4390) [67,294–267,964]
Islet mass transplanted per patient body weight IEQ/kg patient body weight	3314 (1883–4252) [1000[b]–5177]
Islet mass isolated per pancreas mass IEQ/g	3436 (2672–4088) [937[b]–5140]
Total islet pellet volume, in mL	6.5 (4–110) [1.5–22]
In ml/kg patient body weight	0.11 (0.06–0.23) [0.03–0.39]
Number patients who required intraperitoneal completion of islet infusion (*N*)	2 (17%)
Portal venous pressure, mmHg	
Opening	10 (7–11.5) [2–19]
	16 (14–21) [4–35]
Peak	16 (13.5–20) [2–30]
Closing (end of infusion)	17

Table 1 (continued)

Values are expressed as median (IQR), [minimum–maximum] or *N* (percentage)

[a]Negative genetic testing for 5 genes: PRSS1, SPINK 1, CFTR, CTRC, and CASR and no history of CP/RAP in family

[b]In a patient diabetic before TPIAT

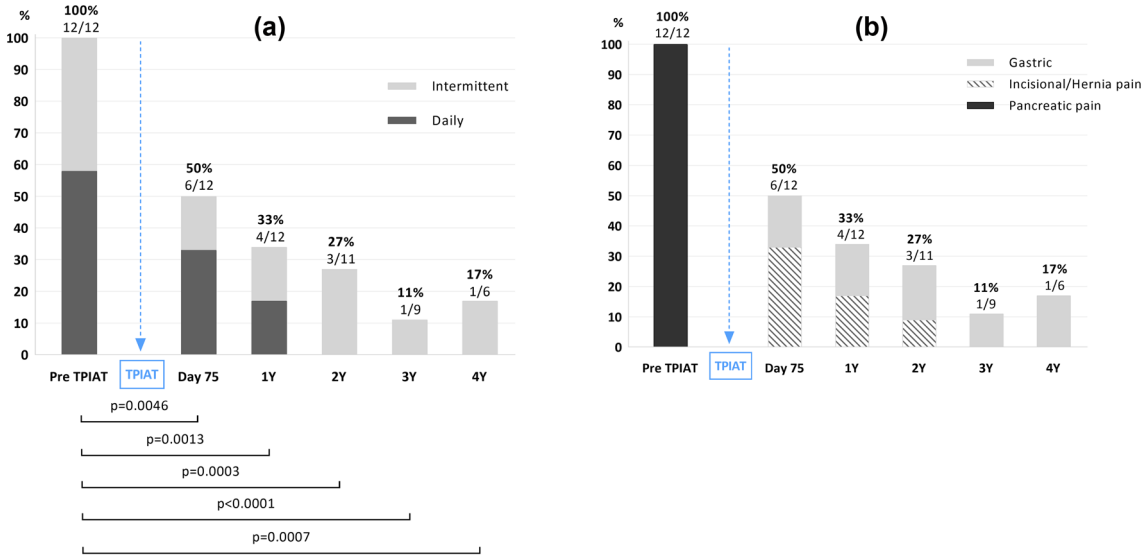

Fig. 1 **A** Patients requiring opioids for pain control. Post-TPIAT, patients experienced a progressive and statistically significant decline in opioid requirements for pain control at each scheduled follow-up as compared to pre-TPIAT ($p < 0.05$). **B** Location of pain requiring opioids. No patients experienced pancreatic-type pain post-TPIAT. All post-TPIAT pain was different from the pre-TPIAT pain and included incisional/hernia-related pain or pain at other locations. Non-pancreatic pain was completely responsible for the opioid requirement post-TPIAT

($\beta = 0.3678$, $p = 0.0026$). At 1 year, 4 (33%) patients still confirmed taking oral opioids, and two (17%) of them requiring daily opioids due to an incisional hernia or idiopathic abdominal pain. Two other (17%) patients needed opioids intermittently due to abdominal wall neuralgia or autoimmune gastritis. All patients with persistent post-TPIAT pain at 1 year were the older patients in our cohort, with a median age of 19.5 years (18–21).

Glycemic control

Post-TPIAT, gradual improvement of glycemic control was observed over the first year which was commensurate with progression of islet engraftment and overall clinical recovery. Nine (75%) patients were insulin-independent at some time point during follow-up: 7/7 (100%) boys and 2/5 (40%) girls (Fisher $p = 0.045$). At the 6-month mark, 50% (6/12) of the patients were insulin-independent with an HbA1c of < 6.5% and that rate was maintained throughout 4 years after the surgery (Fig. 2). Islet graft function as assessed by the BETA-2 score remained stable over time in all insulin-independent patients during follow-up (BETA-2 above 16) (Fig. 3). One patient with relatively high serum c-peptide required a few units of short acting insulin daily, and maintained stable glucose control with an HbA1c of 6.5% at 2 year follow-up. However, the remaining three teenagers had a low serum c-peptide and required full insulin supplementation (insulin pump or short- and long-acting insulin injections) and had poor glucose control with HbA1c ranging between 7.8 and 10% (BETA-2 < 10).

Endocrine success of TPIAT (insulin-independence at 4-year follow-up) was negatively associated with a duration of CP, pre-TPIAT BMI, BMI percentile, and BSA, and positively associated with islet mass (Supplementary Table S1). Endocrine success was not associated with the age at diagnosis, age at operation, BSA percentile, or gender. Multivariate logistic regression confirmed that the duration of CP prior to TPIAT, BMI, BMI percentile, BSA, and HbA1c pre-TPIAT were consistently negatively correlated with the BETA-2 score during follow-up, while the mass of infused islets (IEQ, IEQ/kg) and age of diagnosis were consistently positively correlated (Supplementary Fig. 1). Patients with a lower pre-TPIAT BMI (< 23 kg/m^2) achieved insulin-independence more often, but such a relation for BMI percentile was not statistically significant (Fig. 4). The duration of CP diagnosis pre-TPIAT demonstrated a

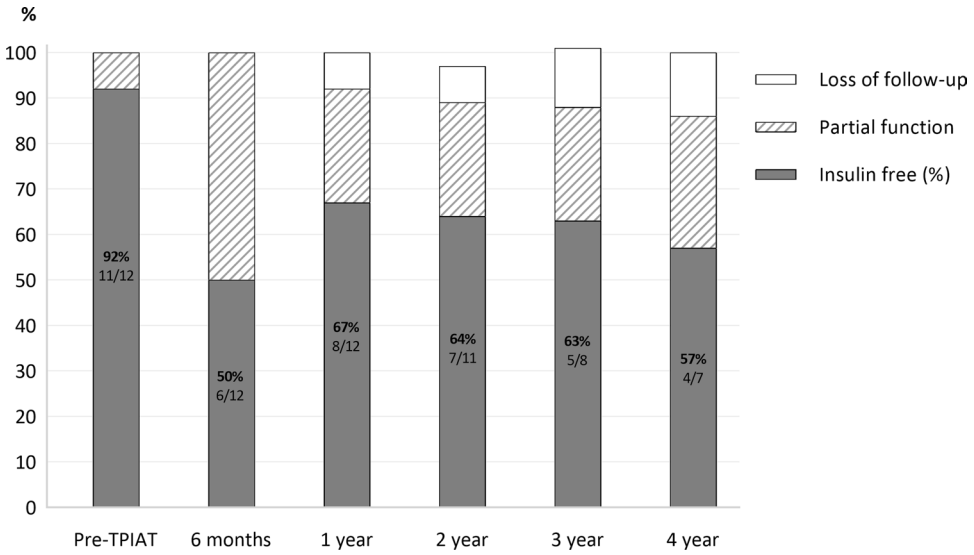

Fig. 2 Glycemic control and insulin requirements after TPIAT. Islet autotransplantation led to gradual improvements in glycemic control as demonstrated by declining HbA1c and insulin requirements, as compared to pre-operative values. This trend continued for 4 years of follow-up

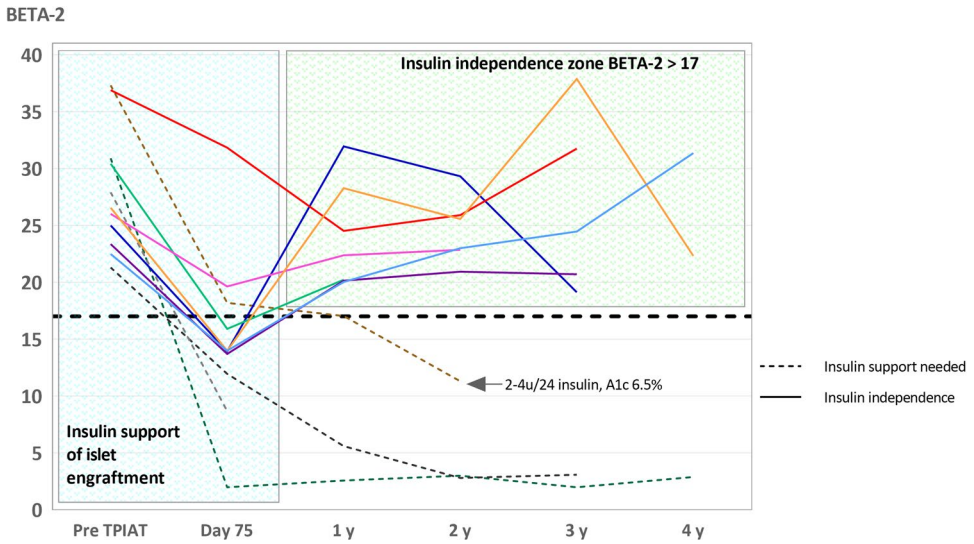

Fig. 3 Islet graft function monitoring based on BETA-2 trajectory after TPIAT. The BETA-2 score in patients who achieved insulin-independence fluctuated over cut off 16, which reflected stable islet graft function during follow-up (continuous line). Patients with partial graft function (dashed line) had a BETA-2 score below the cut off of 16

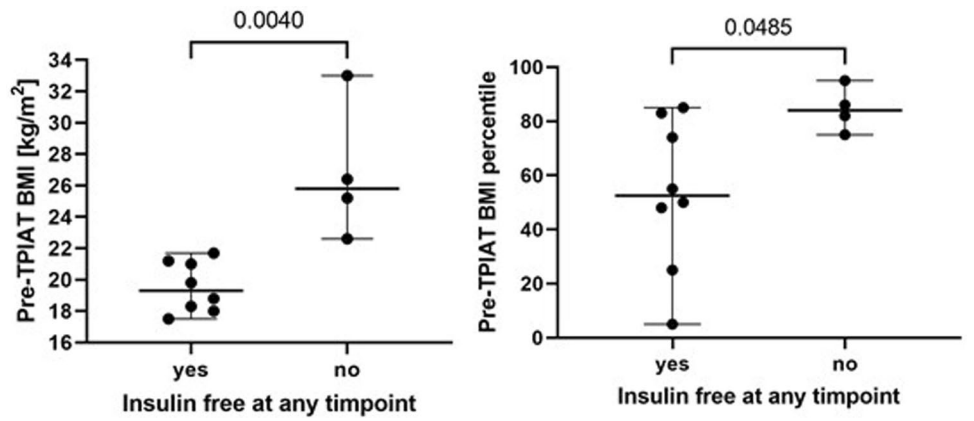

Fig. 4 Pre-TPIAT BMI (kg/m^2), BMI percentile, and post-TPIAT insulin-independence. Patients who became insulin-independent post-TPIAT had a significantly lower pre-TPIAT median BMI and BMI percentile compared to patients with a persistent insulin requirement (UMW $p = 0.0040$, 0.0485)

statistically significant negative correlation with islet yield mass (Fig. 5A, B). Islet yield was lower in patients who suffered longer from CP/ARP prior to TPIAT. Patients who

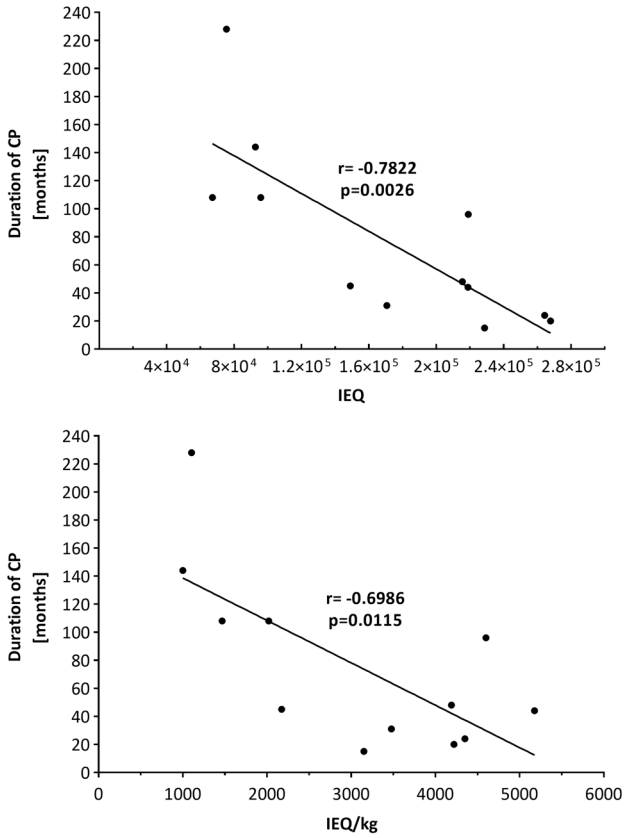

Fig. 5 Duration of chronic pancreatitis (CP) pre-TPIAT is negatively correlated with islet yield: patients who suffered from CP for longer periods of time (measured in months) had lower islet isolation yields. Islet isolation yields were measured as islet mass transplanted in IEQ ($r = -0.782$, $p = 0.003$) (Panel **A**) and IEQ/kg ($r = -0.699$, $p = 0.012$) (Panel **B**)

achieved insulin-independence had received a larger islet dose (Mann–Whitney *U* test, $p = 0.009$, Fig. 6).

Taken all together, patients who suffered from CP for a longer duration prior to TPIAT (≥ 9 years) had lower islet mass isolated, and thus lower islet mass available for transplantation (≤ 2000 IEQ/kg), which made post-TPIAT insulin-independence less likely (OR = 0.0252, 95% CI 0.0008–0.7817, $p = 0.0357$). Moreover, we observed a positive correlation between the BETA-2 score at 1 and 2 years post-transplantation and the transplanted islet mass (Supplementary Fig. 1).

Quality of life

In post-TPIAT surveys, all pediatric patients and their families reported subjectively a substantial improvement in their daily quality of life primarily due to the alleviation of chronic pancreatic pain and the cessation of episodes of recurrent pancreatitis. All patients (12/12) resumed their previous, normal levels of educational, professional, and physical activities. The three oldest patients in this cohort were able to transition to full autonomy independent from their parents. All patients reported an improved quality of life regardless of whether they were insulin-independent or still required some insulin support. The patients and their families described the burden of being diabetic as manageable. Similarly, they reported subjective improvement in chronic pain, and relief from opioid-dependence.

Discussion

Role of TPIAT for pediatric patients with CP and RAP

As the etiology of pancreatitis in children is usually related to deleterious genetic alterations that promote the abnormal activation of pancreatic enzymes throughout the entire organ, targeting ductal strictures in pediatric patients is usually ineffective in the long term. Furthermore, repeat stenting and drainage procedures may lead to recurrent infection and accelerate the progression of organ damage.

TP as a treatment option has been avoided for decades, since patients uniformly become diabetic and suffer from disease sequelae including a severely compromised quality of life. However, progress in islet allo-transplantation and greater experience in islet isolation have led to improved metabolic outcomes in islet auto-transplantation. The first

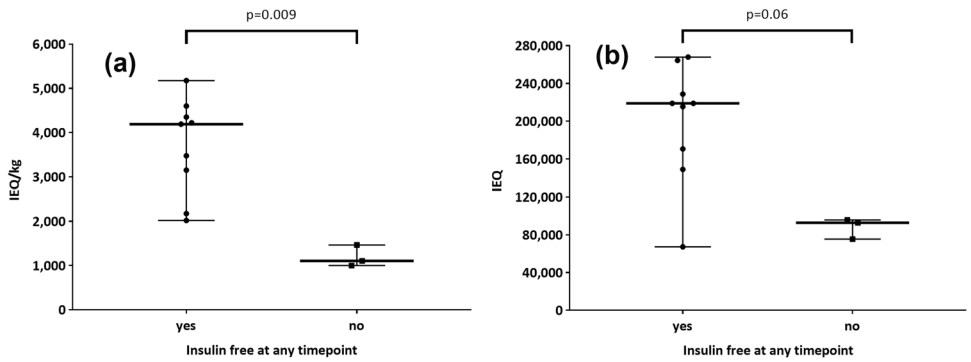

Fig. 6 A higher islet mass at transplantation correlates with insulin-independence: patients who became insulin-independent post-TPIAT had a significantly higher transplanted islet mass, expressed as IEQ/kg (panel **A**) and IEQ (panel **B**), compared to post-TPIAT patients with a persistent insulin requirement. Higher isolated islet yields allowed for transplantation of a higher islet mass

pediatric TPIAT was performed in Minneapolis in 1989, and that center has led the field over the last 30 years [11]. Their experience suggests that optimal clinical outcomes are possible if patients undergo TPIAT prior to developing opioid-dependence, diabetes, or even prediabetes [11].

Regulatory constraints have led to a gradual decline in the field of islet allo-transplantation in adults in the United Stated and the number of islet centers with sufficient expertise in pediatric pancreas processing has shrunk considerably to only three centers (Minneapolis, Cincinnati, and Chicago) [12, 13].

Elimination of pain is the main therapeutic goal

The Minneapolis group has demonstrated that, within the first year post-procedure, over 80% of patients experienced an alleviation of pain without opioid requirements and that these effects were maintained for 10 years of follow-up [11]. We attributed the slightly higher rate of opioid requirements (33%) in our cohort at 1 year to the inclusion of patients seen as children, but who were young adults by the time of operation [11]. Encouragingly, pancreatic pain resolved in all of our patients shortly after surgery. Although some patients suffered from pain related to complications, in all but one patient this pain ultimately resolved by the third post-operative year.

Glycemic control was consistently achieved

Insulin independence was achieved in half of our patients during 4 years of follow-up after pancreatic islet auto-transplantation. Our insulin-independence rates are consistent with those presented by Bellin et al. from the most experienced center [11, 14].

Children as well as adults with an extended overall duration of CP pre-operatively had a lower number of islets retrieved and subsequently auto-transplanted, which directly limited their opportunity to develop insulin-independence [11, 15, 16]. Three-fourths of our patients who received over 2000 IEQ/kg of islet mass became insulin-independent, while none of those who received less met the criteria to cease insulin support. This result parallels that of the Minnesota experience, where historically approximately two-thirds of pediatric patients that received over 5000 IEQ/kg achieved insulin-independence [11]. In our cohort, no patients who were prediabetic or diabetic prior to TPIAT were eligible to stop insulin supplementation similarly to adults reported previously [16]. Interestingly, as in other centers, male pediatric patients in our study had a higher rate of insulin-independence compared to female patients [11, 14]. Using BMI unadjusted for sex and age could incorporate potential bias, and as such, the use of BMI percentile is recommended especially among the pediatric population. High BMI and BMI percentile both are surrogate indicators for an overweight state and obesity which typically increase insulin requirements and reduce the possibility of insulin-independence.

Interestingly, although the BSA was associated with insulin-independence, its percentile rank demonstrated no association. In bivariate logistic regression analysis, lower BSA and higher infused islet mass (IEQ) were associated with insulin-independence, which independently confirms their previously published association [11] (Supplementary Table S1).

Taken together, these findings have very significant clinical implications which may guide patients, their parents, and medical teams toward optimal timing of the decision to pursue TPIAT. Our overall insulin-independence rate after 2 years was 63.6% (7/11), consistent with reports from other institutions (64%) and higher than in the adult population (33%) [17–19]. Importantly, all of our insulin-independent patients maintained optimal islet graft function over time as determined by the BETA-2 score, which verifies clinical stability of the islet graft over time as observed in Minneapolis [11]. Patients with robust partial islet graft function are able to maintain near-optimal glucose control with very low insulin requirements. An overall metabolic benefit of islet auto-transplantation was achieved in 75% of our patients.

However, teenagers and young adults with minimal islet graft function who required full insulin supplementation displayed poor glucose control with an elevated HbA1c, which underscores overall challenges related to compliance in any type of medical therapy in this cohort of relatively young patients.

Overall, our analysis confirmed findings from other leading centers: that delaying operation reduces opportunity for insulin-independence and the possibility of benefiting from islet auto-transplantation. Obesity, female gender, older age, and prediabetes seem to be additional negative prognostic factors for favorable endocrine outcomes. Robust partial islet graft function improves overall glucose control and will likely protect the patient from hypoglycemic unawareness, severe hypoglycemic episodes, and other diabetes-related complications in the future [18].

Surgical technique and other steps to mitigate and manage complications

The leading centers in Minneapolis (UMN) and Cincinnati (UCN) routinely perform splenectomy during pancreatectomy to reduce the likelihood of post-surgical spleen-related complications (i.e., splenic infarction, hemorrhage, and varices) [11, 20]. However, this prophylactic measure is not without risk as splenectomy can lead to thrombocytosis and reduced immunity against encapsulated bacteria. Thrombocytosis, especially extreme forms with platelet counts over

1 M/ml, usually require additional antithrombotic therapy with aspirin or hydroxyurea [11]. Despite using dextran (40,000) followed by aspirin and prophylactic heparin for anticoagulation, UMN reported that 40% of patients required blood product transfusions versus 6% among patients that did not receive dextran [21]. Additionally, 3 children out of 75 (4%) experienced mortality from septic complications. Two developed overwhelming sepsis several years after TPIAT, possibly due to relevant immunologic limitations associated with splenectomy despite appropriate vaccinations [11]. Consequently, antibiotic prophylaxis has been extended to 1 year post-operatively in later patients [11].

Our center opted to avoid splenectomy which was successful in (9/12) 75% of our patients. One (11%) patient developed a splenic infarction 6 months post-TPIAT and required a subsequent splenectomy. In our 9 splenic-preserved patients, we did not identify any early or late sepsis nor any incidence of *Clostridium difficile* infection. Prior to the optimization of anti-thromboembolic prophylaxis and the introduction of intravenous heparin during the first 48 h post-TPIAT, we experienced two episodes of bleeding and one portal vein thrombosis, though there were no bleeding or thrombotic events afterward.

In contrast to UMN and UCN [11, 18, 20], we chose not to place GJ tubes and one-third of our patients required total parental nutrition (TPN) due to prolonged post-operative ileus and/or delayed gastric emptying which was further compounded by intensive opioid therapy.

All of our patients and their parents reported a tremendous improvement in the quality of life of their children several months after the procedure. The elimination of constant abdominal pain and the fear of recurrent pain effectively eliminated or substantially decreased the level of anxiety and depression in our patients. This symptomatic control helped to remove previous dietary and physical restrictions and facilitated a return to daily activities including schooling and work. Improvements in patient quality of life as measured by standardized questionnaires were also reported by other centers [22, 23].

Limitations

We acknowledge significant limitations of our study, since we report results from a single center with a specific patient selection strategy and clinical approach. Our analysis is based on a limited number of patients which limited the power of statistical analysis. Subjectively, our clinical practice pattern appears to be less aggressive with less-extensive surgical activity, including the simultaneous avoidance of splenectomy, gastro-jejunostomy, and appendectomy. We are currently collaborating with other leaders in the field as part of a multi-center trial of TPIAT to recruit a larger number of subjects, including pediatric patients, to validate our current findings and further refine our clinical approach [24].

Conclusion

TPIAT is a viable treatment option for pediatric patients with CP and ARP, and can effectively treat severe, debilitating pain. The significant reduction in pain translates to decreased opioid use and leads to an improved quality of life for patients and their families. Finally, islet auto-transplantation may reliably prevent the development of diabetes in at least half of all pediatric cases with a significant number of patients becoming insulin-independent over time.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00383-021-04956-5.

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