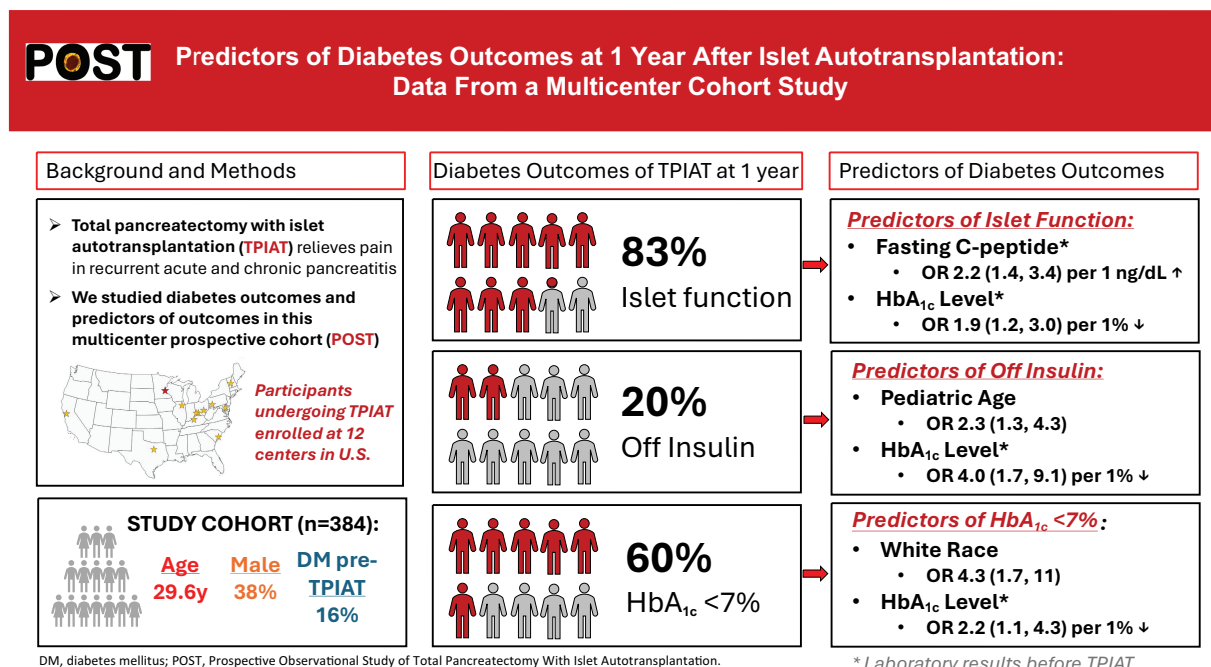


Predictors of Diabetes Outcomes at 1 Year After Islet Autotransplantation: Data From a Multicenter Cohort Study

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ARTICLE HIGHLIGHTS

• Why did we undertake this study?

We performed a large multicenter study to determine diabetes outcomes after total pancreatectomy with islet autotransplantation (TPIAT) (Prospective Observational Study of TPIAT [POST]).

• What is the specific question we wanted to answer?

We assessed the prevalence of insulin independence and islet function, and evaluated potential predictors of diabetes outcomes, glycemic control, and islet function after TPIAT.

• What did we find?

At 1 year post-TPIAT, 83% of patients retained islet function (C-peptide >0.3 ng/mL), 20% were off insulin, and 60% had HbA_{1c} <7%. Younger children, and those without diabetes or with prediabetes before TPIAT had the best outcomes. Pre-TPIAT HbA_{1c} was associated with a higher odds of insulin independence, graft function, and HbA_{1c} <7% at 1 year.

• What are the implications of our findings?

With islet autotransplantation, most patients maintain islet function, and some achieve insulin independence, whereas without autologous islet infusion, transplant alone will always result in complete insulin dependence. When evaluating patients for TPIAT, age, diabetes status, and HbA_{1c} pre-TPIAT are important predictors of outcomes.



Predictors of Diabetes Outcomes at 1 Year After Islet Autotransplantation: Data From a Multicenter Cohort Study

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OBJECTIVE

Total pancreatectomy with islet autotransplantation (TPIAT) may relieve pain for patients with intractable recurrent acute or chronic pancreatitis. In this first multicenter cohort study of TPIAT, we aimed to identify predictors of favorable diabetes outcomes following TPIAT to aid in surgical counseling and decision making.

RESEARCH DESIGN AND METHODS

We included 384 patients (mean [SD] age 29.6 [17.1] years; 61.7% female) who underwent TPIAT and were enrolled in the National Institutes of Health–sponsored multicenter Prospective Observational Study of TPIAT (POST). Outcomes were reported for insulin use, HbA_{1c}, and islet graft function. Univariable and multivariable modeling was performed to evaluate predictors of diabetes outcomes after TPIAT.

RESULTS

At 1 year post-TPIAT, 83% of patients retained islet function (C-peptide >0.3 ng/mL), 20% were off insulin, and 60% had HbA_{1c} <7%. Outcomes were most favorable in those with normoglycemia pre-TPIAT and in children. In multivariable analysis, insulin independence at 1 year was associated with pediatric age (odds ratio [OR] 2.3 [95% CI 1.3–4.3] vs. adults) and pretransplant HbA_{1c} (OR 4.0 [1.7–9.1] per 1% decrease HbA_{1c}). The odds of achieving a goal HbA_{1c} <7% was associated with White race (OR 4.3 [1.7–11]) and pre-TPIAT HbA_{1c} (OR 2.2 [1.1–4.3] per 1% decrease). Islet graft function was associated with pre-TPIAT fasting C-peptide (OR 2.18 [1.42–3.35] per 1 ng/mL increase) and baseline HbA_{1c} (OR 1.89 [1.18–3] per 1% decrease).

CONCLUSIONS

Patients with normoglycemia and children more often were off insulin. In multivariable models, pre-TPIAT HbA_{1c} was strongly predictive of insulin independence, islet function, and HbA_{1c} <7% at 1 year.

Total pancreatectomy with islet autotransplantation (TPIAT) is a surgical treatment offered to selected patients with disabling recurrent acute or chronic pancreatitis (1,2). For affected patients who have not responded to other treatments, TPIAT

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See accompanying article, p. 1475.

offers a chance for pain relief and improved quality of life (3–6). In this procedure, the entire pancreas is resected, and the islets are isolated by enzymatic and mechanical digestion of the pancreas *ex vivo* and autologously transplanted intrahepatically via infusion into the portal vein (7,8). Most patients do not have diabetes before pancreatectomy. Thus, the islet autotransplant serves a secondary purpose: to mitigate the severity of postpancreatectomy diabetes. For ~20–30% of patients, the transplanted islet mass and function is sufficient to achieve insulin independence, often for years after operation (5,9).

While TPIAT diabetes outcomes have been previously reported (9–16), the majority of this work is restricted to single-center cohorts and often uses data collected from medical records, thus introducing potential bias from missing data or nonstandardized documentation in medical charts. While all patients undergoing TPIAT must be willing to accept the risk for diabetes, uncertainty with regard to individual diabetes risk is a great source of trepidation for patients and providers. Patient age; parameters that signal low islet mass, such as pancreatic calcifications and prior partial pancreatic resections; and laboratory values before TPIAT have been previously cited as potential predictors of diabetes outcomes (5,17).

The multicenter Prospective Observational Study of TPIAT (POST) Study Consortium was formed in 2015 to conduct a prospective multicenter study of TPIAT outcomes and was funded by the National Institute of Digestive and Diabetes and Kidney Diseases (18,19). By providing dedicated research coordinators and database support and predefined follow-up intervals, the POST study harmonized standardized preoperative, surgical, and postoperative outcomes data collection from children and adults who underwent TPIAT at 12 centers, with the intention to better define outcomes after TPIAT and determine factors that may be particularly important in predicting outcomes in this population.

The primary objective of the analyses reported herein was to determine measurable preoperative factors that best predict diabetes outcomes at 1 year after TPIAT, defined by insulin use, islet graft function, and glycemic control. Additionally, we evaluated independent

associations of transplanted islet mass and other islet graft characteristics, which are only measured at the time of TPIAT, with diabetes outcomes.

RESEARCH DESIGN AND METHODS

Study Design and Participants

POST is a multicenter cohort study that enrolled participants undergoing TPIAT for chronic or recurrent acute pancreatitis between January 2016 and March 2022 at 12 participating clinical centers (18). Patients were deemed candidates for TPIAT based on the clinical evaluation protocols of the evaluating centers. Patients undergoing a total or completion pancreatectomy with islet autotransplant were eligible (18). Data were collected through medical records, participant interview, and standardized questionnaires within 3 months before TPIAT and at 6 months and 1 year after TPIAT.

The protocol was reviewed and approved by each center's institutional review board. Informed consent or parental consent and patient assent, as age appropriate, were obtained. The protocol, case report forms, and standard operating procedures for the POST Study Consortium are publicly accessible (<https://z.umn.edu/poststudy>).

Surgical Approach

TPIAT was performed by experienced surgeons and islet isolation facilities at each center. Total pancreatectomy and duodenectomy are performed, and intestinal and biliary continuity are restored using various approaches, most often involving a Roux-en-Y reconstruction. Surgical approaches and complications have been previously published (2). Islet isolation occurred via intraductal injection of a collagenase solution, followed by mechanical disruption using the semiautomated Ricordi method (8), with COBE purification as deemed necessary for high tissue volume. Islet isolation outcomes were previously described for this cohort (7). Islets were then transplanted fresh into the portal vein, with other sites used more rarely if complete infusion into the portal vein was contraindicated (e.g., in cases of significant intraportal hypertension during infusion).

Medical History Prior to TPIAT and at Surgery

Before TPIAT, standardized data were collected from medical records and

direct participant report for pancreatitis onset, prior treatments, etiologies of pancreatitis, history of diabetes, and other medical comorbidities. Medication history was collected from participants for use of insulin, any diabetes medication, and opioid use. Preoperative laboratory test results were abstracted from the medical record, including HbA_{1c}, fasting glucose, and fasting C-peptide levels. Diabetes was defined by prior diagnosis of diabetes at time of enrollment, fasting glucose ≥ 126 mg/dL, HbA_{1c} $\geq 6.5\%$, or insulin or noninsulin medication specifically to treat diabetes. Prediabetes was defined by pre-TPIAT HbA_{1c} 5.7–6.4% or fasting glucose 100–125 mg/dL.

At the time of TPIAT, surgical and islet transplant details were collected (7). Islet mass was quantified using the standard approach and expressed as total islet equivalents (IEQ) and islet equivalents per kilogram body weight (IEQ/kg).

Outcomes at 6 Months and 1 Year

Outcomes collected for diabetes from the participant included insulin use, insulin regimen (pump, multiple daily injections, or basal insulin), 14-day average daily insulin dose, noninsulin medication use, and any severe hypoglycemic episodes (defined as participant-reported loss of consciousness, seizure, need to take emergency glucagon, or paramedic call). We collected laboratory results from routine clinical follow-up for HbA_{1c}, fasting C-peptide, and fasting glucose. We conservatively defined islet graft function as a fasting C-peptide ≥ 0.3 ng/mL and graft failure as fasting C-peptide < 0.3 ng/mL (20). Additional metrics were collected for quality-of-life and pain outcomes and have been reported separately (21). Due to the geographic distribution of TPIAT recipients, post-TPIAT study visits could occur in person or virtually.

Statistical Analysis

Participants were included if they had data available at 6 months and/or 1 year after TPIAT. Summary data and outcomes were reported as means and SDs, or numbers and percentages of participants. Differences between baseline and 1-year outcomes were tested using paired *t* tests or McNemar tests. Linear and logistic regression models were used to evaluate associations between risk factors of interest and 1-year diabetes outcomes, including

insulin independence, insulin dose, HbA_{1c}, HbA_{1c} <7%, fasting C-peptide, and islet graft function. Insulin dose and fasting C-peptide were log-transformed to reduce skew. Prior to transformation, the 2.5th percentile was added to all values to avoid taking the log of 0 and near-zero values.

Regression modeling was done in two phases. The first set of regression models comprised univariable and multivariable models that considered only variables that are measurable before TPIAT. Random forests were used to select variables to be included in multivariable models. Age-group (adult vs. child) was included in all models. For each outcome, candidate variables were included in a random forest with 500 trees, and variable importance was calculated based on mean decrease in accuracy for categorical outcomes and percent increase in mean squared error for continuous outcomes. *P* values were calculated using a permutation test, with the null distribution of variable importance estimated using 250 permutation replicates. Variables with the smallest *P* values were selected for the multivariable model with the following limitations: 1) the number of variables was limited to maintain 10 observations per variable (linear regression) or events per variable (logistic regression), and 2) only variables with *P* < 0.2 were included. The selected variables were used to fit a final multivariable mixed-effects model with a random effect for site to account for variability in outcomes across sites. The second set of regression models comprised univariable models with islet graft characteristics (IEQ transplanted, IEQ/kg transplanted) as the independent variable. A two-sided *P* < 0.05 was considered significant. All analyses were conducted using R statistical software.

RESULTS

Cohort Characteristics and Overall Outcomes

Among 405 participants who met initial eligibility criteria and underwent TPIAT, 384 had follow-up data (94.8%) and were included in the analysis for this report. Patients had a mean (SD) age of 29.6 (17.1) years (*n* = 129 children and 255 adults), and 237 (61.7%) were female. Most were White and non-Hispanic, and genetic risk factors for pancreatitis were

identified in 86% of children and 49% of the adults (Table 1). Sixty participants (16.6%) had a pre-TPIAT diagnosis of diabetes, and 39 (10.2%) were on insulin pre-TPIAT, typically at a low dose.

At 6 months after TPIAT, 12% of patients were off insulin, increasing to 20% at 1 year (Table 2). The overall mean (SD) daily dose was 0.37 (0.47) and 0.34 (0.36) units/kg/day at 6 months and 1 year, respectively. Mean (SD) HbA_{1c} levels were 6.6% (1.5%) and 7.0% (1.9%) at 6 months and 1 year, respectively. Most patients had islet graft function (82.9% at 1 year). Although the primary end point of this study was 1-year outcomes, results for participants followed up at 2–4 years post-TPIAT suggested improving insulin independence rates (27–30% of participants) with stable islet graft function in ≥84% at each time point (Supplementary Table 1). Severe hypoglycemia was reported by 5.8% before and 14.2% after TPIAT but was not related to islet function or insulin use (Supplementary Table 2).

Diabetes Outcomes Based on Diabetes, Prediabetes, or Normoglycemic Status at the Time of TPIAT and by Pediatric or Adult Age

Having diabetes or prediabetes before TPIAT was associated with less-favorable 1-year outcomes for insulin use, glycemic control, and islet function. Among participants with presurgical diabetes, 4% were off insulin at 6 months; however, all were on insulin by 1 year post-TPIAT. Of those meeting prediabetes laboratory criteria prior to TPIAT, 8 of 92 (9%) and 13 of 91 (14%) were off insulin at 6 months and 1 year post-TPIAT, respectively. In contrast, 15% (27 of 176) of participants with normoglycemia pre-TPIAT were insulin free at 6 months and 27% (48 of 180) at 1 year post-TPIAT (22% of adults and 33% in children, respectively; *P* < 0.0001 for difference in 1-year insulin use rate by diabetes status before surgery).

Similarly, target HbA_{1c} <7% and having islet graft function were most likely in the group that did not have diabetes or prediabetes before TPIAT (*P* < 0.0001 for both comparisons at 1 year). For islet graft function, only 7% of patients with normoglycemia had islet graft failure at 1 year compared with 22% in those with prediabetes and 49% in those with

diabetes (*P* < 0.0001) (Supplementary Table 3).

Compared with adults, children were more likely to be off insulin (33% vs. 13%, *P* < 0.0001), at goal HbA_{1c} (76% vs. 51%, *P* < 0.0001), and with retained islet graft function (91% vs. 78%, *P* = 0.0066) at 1 year post-TPIAT (Supplementary Table 3).

Pre-TPIAT Predictors of Outcomes: Univariable Analyses

One major aim of the POST study was to determine whether factors that are measurable before TPIAT can predict insulin use, islet graft function, and other diabetes outcomes after TPIAT. We focused on three outcome categories: 1) insulin use and dose, 2) glycemic control by HbA_{1c}, and 3) islet graft function by C-peptide. Associations in univariable analyses incorporating sex, age, race and ethnicity, weight status, pancreatitis factors, pre-operative diabetes status and testing, and lifestyle factors are summarized in Supplementary Tables 4 and 5.

Multivariable Models for Diabetes Outcomes 1 Year Post-TPIAT

Predictors of Insulin Independence

Because all participants with preoperative diabetes were on insulin at 1 year post-TPIAT, we excluded these individuals in the multivariable model. In multivariable modeling for insulin-free status at 1 year post-TPIAT, pediatric age versus adult age and baseline HbA_{1c} emerged as significant predictors, with an odds ratio (OR) of 2.3 (95% CI 1.3–4.3) for pediatric patients and 4.0 (1.7–9.1) per 1% decrease in HbA_{1c} (Table 3). Presurgical C-peptide was not associated with insulin independence.

For adult participants with pre-TPIAT HbA_{1c} <5.7%, the proportion who were insulin independent was 19% at 1 year, and HbA_{1c} 5.7–6.2% was 2.5%. For children, the same insulin-free rates were 34% and 23%, respectively. No patients were off insulin at 1 year when HbA_{1c} was >6.2% prior to surgery (Supplementary Tables 6 and 7).

Predictors of Glycemic Control (HbA_{1c})

In multivariable modeling for reaching target HbA_{1c} <7%, the odds of achieving a goal HbA_{1c} <7% was higher with White race (OR 4.3 [95% CI 1.7–11]) and with a lower pre-TPIAT HbA_{1c} level (OR 2.2 [1.1–4.3] per 1% decrease in HbA_{1c}). In contrast, there were strong

Table 1—Demographics and clinical history of the study participants

Characteristic	All participants	Children (age <18 years)	Adults (age ≥18 years)
<i>n</i>	384	129	255
Female	237 (61.7)	72 (55.8)	165 (64.7)
Age (years)	29.6 (17.1)	11.6 (4.0)	38.7 (13.5)
Race			
White/Caucasian	351 (91.4)	119 (92.2)	232 (91.0)
Asian	7 (1.8)	1 (0.8)	6 (2.4)
Black/African American	8 (2.1)	1 (0.8)	7 (2.7)
Native Hawaiian/Pacific Islander	2 (0.5)	0 (0.0)	2 (0.8)
American Indian/Alaska Native	2 (0.5)	1 (0.8)	1 (0.4)
Mixed race	12 (3.1)	5 (3.9)	7 (2.7)
Don't know/declined to answer	2 (0.5)	2 (1.6)	0 (0.0)
Hispanic ethnicity	36 (9.4)	13 (10.1)	23 (9.0)
BMI (kg/m ²)	—	—	26.03 (5.22)
BMI percentile	—	68.45 (26.35)	—
Overweight/obesity	184 (47.9)	49 (38.0)	135 (52.9)
Risk factors for pancreatitis			
Toxic/metabolic	51 (13.3)	2 (1.6)	49 (19.3)
Idiopathic	43 (11.2)	2 (1.6)	41 (16.1)
Genetic mutation*	236 (61.5)	111 (86.0)	125 (49.0)
Autoimmune	6 (1.6)	2 (1.6)	4 (1.6)
History of recurrent AP or severe AP	284 (74.2)	108 (83.7)	176 (69.3)
Pancreas divisum	81 (21.1)	25 (19.4)	56 (22.0)
Sphincter of Oddi dysfunction	25 (6.5)	0 (0.0)	25 (9.8)
Other obstructive	9 (2.3)	4 (3.1)	5 (2.0)
Duration of symptoms (years pre-TPIAT)	8.27 (7.6)	5.0 (3.8)	9.9 (8.5)
Duration of diagnosed pancreatitis (years pre-TPIAT)	6.9 (6.9)	4.0 (3.5)	8.4 (7.7)
TPIAT indication			
Recurrent AP only	57 (14.9)	20 (15.5)	37 (14.6)
CP only	169 (44.1)	46 (35.7)	123 (48.4)
Both recurrent AP and CP	157 (41.0)	63 (48.8)	94 (37.0)
Ever had acute pancreatitis	334 (87.2)	126 (97.7)	208 (81.9)
Prior pancreatic surgery	58 (15.1)	7 (5.4)	51 (20.1)
Any ERCP	291 (76.0)	96 (74.4)	195 (76.8)
Number of ERCPs**	4.4 (8.9)	3.3 (2.4)	5.0 (10.7)
Presurgical diagnosis of exocrine insufficiency	137 (35.7)	48 (37.2)	89 (34.9)
Presurgical diabetes status			
None	197 (54.4)	81 (69.2)	116 (47.3)
Prediabetes	105 (29.0)	28 (23.9)	77 (31.4)
Diabetes	60 (16.6)	8 (6.8)	52 (21.2)
Smoking history			
Never	262 (68.2)	129 (100)	133 (52.2)
Former	94 (24.5)	0 (0.0)	94 (36.9)
Current	28 (7.3)	0 (0.0)	28 (11.0)
Any alcohol history (including social drinking)			
No	181 (47.1)	128 (99.2)	53 (20.8)
Yes	203 (52.9)	1 (0.8)	202 (79.2)
Alcohol dependency			
No	368 (95.8)	128 (99.2)	240 (94.1)
Yes	15 (3.9)	1 (0.8)	14 (5.5)
Declined to answer	1 (0.3)	0 (0.0)	1 (0.4)
Family history of diabetes			
None	120 (31.2)	35 (27.1)	85 (33.3)
First-degree relative	34 (8.9)	11 (8.5)	23 (9.0)

Continued on p. 1497

Table 1—Continued

Characteristic	All participants	Children (age <18 years)	Adults (age ≥18 years)
Second-degree relative	136 (35.4)	53 (41.1)	83 (32.5)
Both first- and second-degree relatives	94 (24.5)	30 (23.3)	64 (25.1)
Pre-TPIAT HbA _{1c} level (%)	5.61 (1.07)	5.35 (0.79)	5.74 (1.16)
Pre-TPIAT fasting glucose (mg/dL)	99.6 (28.5)	95.5 (25.1)	101.6 (29.8)
Pre-TPIAT fasting C-peptide (ng/mL)	2.01 (1.47)	1.70 (1.37)	2.16 (1.50)
Total IEQ transplanted	258,530 (177,774)	246,210 (154,481)	264,762 (188,446)
IEQ/kg transplanted	4,294 (3,458)	5,653 (4,588)	3,606 (2,451)

Data are mean (SD) or *n* (%). Overweight/obesity was defined as BMI ≥25 kg/m² for adults and age/sex-specific BMI percentile ≥85 for children. AP, acute pancreatitis; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiography. *Genetic testing was completed clinically in all children but in only 71% of adults. **Of those with at least one ERCP.

trends toward not meeting goal HbA_{1c} in former (OR 0.45 [0.21–0.96]) or current (OR 0.42 [0.13–1.39]) tobacco smokers and in adult participants (OR 0.41 [0.17–1.01]) (Table 4).

In multivariable models with HbA_{1c} levels as a continuous variable at 1 year post-TPIAT, HbA_{1c} levels were higher

with higher baseline HbA_{1c}. In the multivariable model adjusted for pediatric or adult age, any lifetime exposure to alcohol was associated with lower HbA_{1c}.

Predictors of Islet Graft Function

In multivariable models for islet graft function, defined as C-peptide ≥0.3 ng/mL,

only two factors were identified as independently associated with islet graft function: pre-TPIAT baseline fasting C-peptide (OR 2.18 [95% CI 1.42–3.35] per 1 ng/mL increase in C-peptide) and baseline HbA_{1c} (OR 1.89 [1.18–3] per 1% decrease in HbA_{1c}). Fasting C-peptide level as a continuous variable

Table 2—Diabetes outcomes after TPIAT

Outcome	Pre-TPIAT	6 Months	1 Year	<i>P</i>
<i>n</i>	384	376	363	
Insulin in past 14 days	39 (10.2)	302 (87.8)	270 (80.1)	<0.001
Insulin regimen*				<0.001
Insulin pump	5 (12.8)	114 (37.7)	125 (46.3)	
Multiple daily injections	22 (56.4)	162 (53.6)	117 (43.3)	
Once daily	12 (30.8)	26 (8.6)	28 (10.4)	
Insulin dose (units/day)**	5.41 (26.28)	23.74 (28.48)	22.54 (25.64)	<0.001
Insulin dose (units/kg/day)**	0.06 (0.29)	0.37 (0.47)	0.34 (0.36)	<0.001
Insulin dose <0.5 units/kg/day**	367 (95.6)	261 (75.9)	248 (74.0)	<0.001
Noninsulin medication for diabetes	15 (3.9)	12 (3.5)	11 (3.3)	1.0
HbA _{1c} level (%)	5.61 (1.07)	6.64 (1.51)	7.02 (1.93)	<0.001
HbA _{1c} <7%	341 (93.2)	231 (67.2)	204 (60.4)	<0.001
Fasting glucose (mg/dL)	99.6 (28.5)	123.4 (55.3)	130.4 (61.4)	<0.001
Fasting C-peptide (ng/mL)	2.01 (1.47)	0.96 (0.79)	0.98 (0.79)	<0.001
C-peptide ≥0.3 ng/mL***	361 (97.6)	256 (84.8)	252 (82.9)	<0.001
Any severe hypoglycemia episodes in past year	22 (5.8)	NA	46 (14.2)	<0.001
Severe hypoglycemia episodes per year (<i>n</i>)	0.23 (1.54)	NA	0.79 (3.74)	0.003
Overall survival at 1 year\$	NA	NA	98.3	NA

Data are mean (SD) or *n* (%). For insulin use, *n* = 384 pre-TPIAT, 344 at 6 months, and 337 at 1 year. For HbA_{1c}, *n* = 366 pre-TPIAT, 344 at 6 months, and 338 at 1 year. For fasting glucose, *n* = 375 pre-TPIAT, 319 at 6 months, and 323 at 1 year. For fasting C-peptide, *n* = 370 pre-TPIAT, 302 at 6 months, and 304 at 1 year. For severe hypoglycemia, *n* = 384 pre-TPIAT and 324 at 1 year. *P* value is for change from baseline to 1 year. NA, not applicable. *Among insulin users only. **Included both users and noninsulin users (at a dose of 0 units/day). ***When 1-year analyses excluded participants with fasting glucose <80 mg/dL (*n* = 29), islet function based on C-peptide ≥0.3 ng/mL was present in 86% of the cohort. \$Overall mortality at 1 year included death ascertainment for all participants who underwent TPIAT, whether they returned for subsequent follow-up. Of 405 participants who underwent TPIAT (including those without follow-up visits), 7 died by 1 year post-TPIAT (1-year survival 98.3%, 1 death at <90 days). None had diabetes recorded as a cause of death, although one participant had metabolic acidosis and encephalopathy as a cause of death.

Table 3—Multivariable model for predictors of insulin use (among participants without pre-TPIAT diabetes) and insulin dose (among insulin users) at 1 year post-TPIAT

	OR (95% CI)	P
Multivariable model of insulin independence (off insulin) at 1 year post-TPIAT		
Baseline HbA _{1c} (%)	0.25 (0.11–0.59)	0.002
Hispanic (vs. non-Hispanic)	1.59 (0.6–4.2)	0.35
Recurrent acute pancreatitis only (vs. CP or CP + RAP)	1.68 (0.79–3.57)	0.18
Adult (vs. child)	0.43 (0.23–0.79)	0.006
Multivariable model for insulin dose at 1 year post-TPIAT in insulin users only*		
Baseline HbA _{1c} (%)	1.07 (0.92–1.24)	0.37
Female (vs. male)	0.66 (0.55–0.80)	<0.0001
Presurgery diabetes status		
Prediabetes (vs. no diabetes)	1.13 (0.87–1.48)	0.35
Diabetes (vs. no diabetes)	1.79 (1.24–2.58)	0.002
Family history of diabetes (vs. no family history)	1.08 (0.88–1.33)	0.46
Adult (vs. child)	0.93 (0.74–1.17)	0.53
Baseline fasting glucose, per 10 mg/dL increase	1.01 (0.96–1.06)	0.68
Non-White (vs. White)	1.47 (1.05–2.05)	0.026

Because all participants with pre-TPIAT diabetes were on insulin after TPIAT, the analysis for insulin independence was restricted only to those without diabetes before TPIAT (representing ~90% of the cohort). All participants on insulin are included in the model for insulin dose, including those with diabetes before TPIAT. RAP, recurrent acute pancreatitis. *Data are ratio of geometric means (95% CI).

at 1 year post-TPIAT was lower in adults (18% lower [95% CI 14–40%]), in those with presurgical diabetes (34% lower [5–54%]) or prediabetes (24% lower [4–40%]), and in those with a family history of diabetes in a first- and/or second-degree relative (11% lower [4–32%]), while it was higher in those with a higher fasting C-peptide before TPIAT (18% higher [10–26%] per 1 ng/mL) (Supplementary Table 8).

Table 4—Multivariable model for predictors of glycemic control by HbA_{1c}, as a continuous value, and proportion of participants with a goal HbA_{1c} <7% at 1 year post-TPIAT

	Coefficient (95% CI)	P
Multivariable model for HbA _{1c} level at 1 year post-TPIAT		
Adult (vs. child)	0.59 (–0.05 to 1.24)	0.073
Female (vs. male)	–0.22 (–0.61 to 0.17)	0.27
Overweight/obesity (vs. no overweight/obesity)	0.13 (–0.26 to 0.52)	0.51
Baseline HbA _{1c} (%)	0.56 (0.3 to 0.82)	<0.0001
Smoking status		
Former (vs. never)	0.39 (–0.16 to 0.93)	0.17
Current (vs. never)	0.96 (0.05 to 1.87)	0.04
PRSS1 positive (vs. negative/not done)	–0.13 (–0.6 to 0.35)	0.60
CFTR positive (vs. negative/not done)	–0.09 (–0.51 to 0.32)	0.65
Presurgery insulin use (vs. no presurgery insulin use)	0.39 (–0.47 to 1.25)	0.37
≥12 Alcoholic beverages in lifetime (vs. <12)	–0.72 (–1.32 to –0.12)	0.02
Multivariable model for achieving HbA _{1c} <7% at 1 year post-TPIAT*		
Adult (vs. child)	0.41 (0.17 to 1.01)	0.05
Nonwhite (vs. White)	0.23 (0.09 to 0.59)	0.002
Overweight/obesity (vs. no overweight/obesity)	0.74 (0.43 to 1.29)	0.29
Smoking status		
Former (vs. never)	0.45 (0.21 to 0.96)	0.038
Current (vs. never)	0.42 (0.13 to 1.39)	0.16
≥12 Alcoholic beverages in lifetime (vs. <12)	1.67 (0.73 to 3.81)	0.22
PRSS1 positive (vs. negative/not done)	1.2 (0.59 to 2.45)	0.62
SPINK1 positive (vs. negative/not done)	0.85 (0.43 to 1.69)	0.65
Disease duration (years)	1.04 (0.99 to 1.09)	0.11
Baseline fasting C-peptide (ng/mL)	0.99 (0.83 to 1.18)	0.90
Baseline HbA _{1c} (%)	0.45 (0.23 to 0.88)	0.02
Baseline fasting glucose, per 10 mg/dL increase	0.94 (0.8 to 1.1)	0.44
Presurgery diabetes status		
Prediabetes (vs. no diabetes)	0.6 (0.27 to 1.36)	0.22
Diabetes (vs. no diabetes)	0.98 (0.26 to 3.63)	0.98
Family history of diabetes (vs. no family history)	1.6 (0.6 to 4.29)	0.34

*Data are OR (95% CI).

Predictors of Insulin Dose at 1 Year After Surgery

Among all insulin users, insulin dose was higher in males (52% higher [95% CI 25–82%]), non-White participants (47% higher [5–105%]), and participants with diabetes before TPIAT (79% higher [24–158%] vs. those with neither diabetes nor prediabetes) (Table 3).

Islet Mass Transplanted and Outcomes After TPIAT

Islet mass and islet number are not known until after pancreatectomy and islet isolation are performed. We therefore did not incorporate islet graft measures into our multivariable models but examined the impact of these separately on diabetes outcomes. Both total IEQ transplanted and IEQ/kg transplanted were strongly associated with insulin use and dose, glycemic control by HbA_{1c}, fasting C-peptide, and islet graft function after TPIAT (Supplementary Table 9). In general, for each 1,000 IEQ/kg more transplanted, the odds of insulin independence increased by 49% (OR 1.49 [95% CI 1.33–1.69]), the odds of reaching goal HbA_{1c} was increased by 38% (OR 1.38 [1.25–1.55] for HbA_{1c} <7%), and the odds for having islet graft function went up by 38% (OR 1.38 [1.19–1.63] for islet function) ($P < 0.0001$ for all). However, these relationships were not linear, with insulin dependence nearly universal with <2,500 IEQ/kg transplanted, and conversely, the majority of participants with >1,000 IEQ/kg transplanted had islet function (Supplementary Fig. 1). Insulin independence at 1 year post-TPIAT was seen in 2% (2 of 110) of participants transplanted with <2,500 IEQ/kg, 12% (15 of 122) with 2,500–5,000 IEQ/kg, and 48% (50 of 105) with >5,000 IEQ/kg, with insulin independence rates only exceeding 50% once a threshold of >6,000 IEQ/kg was reached.

Islet size index is calculated by dividing the islet mass by the islet number, with a ratio >1 indicating more large islets and a ratio <1 indicating more small islets. In multivariable models adjusted for transplanted IEQ/kg, all islets were transplanted intraportally, and COBE step, a higher islet size index was associated with a higher insulin dose ($P = 0.028$) and a lower fasting C-peptide ($P = 0.032$).

CONCLUSIONS

In this multicenter, prospective study following nearly 400 patients who underwent TPIAT for recurrent acute or chronic pancreatitis, the majority had preserved islet graft function after surgery, and ~20% were off insulin by 1 year after TPIAT. Approximately 60% were meeting American Diabetes Association goals for good glycemic control (HbA_{1c} <7%) at 1 year, and daily insulin doses were relatively low (~0.34 units/kg/day). While many preoperative factors were associated with diabetes outcomes, in multivariable modeling, pediatric versus adult age and lower preoperative HbA_{1c} were strongly associated with insulin use, glycemic control, and islet graft function. Pre-TPIAT fasting C-peptide was strongly predictive of postoperative C-peptide and having islet function (vs. failure). These results support the value of assessing glycemia and islet function before TPIAT as part of the evaluation and counseling process.

Perhaps among the most important observations in this multicenter study is that we validated the insulin independence and glycemic outcomes previously reported from single centers, supporting the benefit of an islet autotransplantation when transplant is performed (4,6,15). Although 80% of participants remained on insulin at 1 year, this was expected since a portion of the islets are lost during isolation and from the instant blood-mediated inflammatory response after infusion (22–25). Insulin is weaned slowly after islet autotransplantation as islets engraft, and patients gradually recover to full physical health (15). Our long-term outcomes, albeit available for a smaller proportion of the cohort, suggest that insulin independence rates are higher >1 year after surgery, approaching 30% of patients being off insulin at ≥2 years. These results are similar to the only other multicenter study published in TPIAT, which was a randomized trial with fewer centers and ~75% fewer participants than our current study. That trial observed 20% of patients being off insulin at 1 year (22).

Importantly, regardless of insulin use, >80% of TPIAT recipients maintained islet graft function (C-peptide ≥0.3 ng/mL), and mean HbA_{1c} at 1 year post-TPIAT was 7%. These are patients who without an islet autotransplantation would have had

complete insulin deficiency from pancreatectomy. Preservation of C-peptide in type 1 diabetes is associated with improved long-term diabetes health (26). Performing the islet autotransplantation introduces very little additional medical risk beyond the pancreatectomy, as patients receive their own islets and no immunosuppression is required.

Children fared particularly well after TPIAT. Compared with adults, children had more than twice the odds of having islet graft function, discontinuing insulin, and meeting glycemic control goals (HbA_{1c} <7%) at 1 year post-TPIAT. This finding is consistent with prior studies in children, particularly in young children (28). While reasons are not entirely clear, this may reflect more healthy/resilient islets, tight glycemic management (with parental oversight), less overweight/obesity in children versus adults in our cohort, and/or a generally healthier pancreas from intervention at a younger age. While not a focus of this analysis, children also have robust outcomes for pain remission and quality-of-life improvement (21,27–29). Thus, although providers may be reluctant to refer a young child for such a major intervention, the data support that TPIAT should be at least considered in children who are struggling with pain and hospitalizations due to intractable pancreatitis.

Of note, participants with diabetes before surgery (who comprised ~15% of this cohort) were never off insulin at 1 year and required a higher dose of insulin after TPIAT. These individuals still had islet function preserved approximately half of the time, which is similar to that reported in a small, single-center study (30). Considering that not performing islet autotransplantation would lead to complete loss of islet function, TPIAT may be considered for patients who have preexisting diabetes but have documented evidence of islet function to preserve islet mass. However, patients and providers should be aware that islet transplantation will not be successful at preserving islet function in some cases. In contrast, in another study, individuals with prediabetes did have islet graft function in nearly 80% and insulin independence in 14% of patients at 1 year (16). Although timing for intervening with TPIAT must depend primarily on pain burden and disability from pancreatitis, these findings highlight the potential

advantages of proceeding to TPIAT before metabolic function is significantly compromised.

In multivariable modeling accounting for multiple patient and disease variables, pre-TPIAT HbA_{1c} emerged as an important predictor of all major outcomes, including insulin independence, islet function, and HbA_{1c}, and fasting C-peptide was strongly associated with islet function. In addition, pediatric versus adult age was strongly related to outcomes. Female sex was associated with lower insulin needs. Non-White race was associated with both higher insulin doses and lower odds for achieving the goal HbA_{1c}, which may represent differences in insulin sensitivity, HbA_{1c} assay performance, or differential access to care, similar to disparities reported in other diabetes populations (31). However, it should be noted that only 8% of our cohort was non-White, so these differences should be interpreted with caution. Interestingly, other factors such as calcifications that we previously observed to be associated with low islet yield in POST (7) and that have been associated with insulin dependence in other single-center reports (15,32–35) did not appear as significant in our multivariable model. We theorize that these other patient and disease factors were strongly associated with age and/or baseline glycemic status and, thus, no longer emerged in multivariable modeling once accounting for these other factors. It is likely that they are still clinically important but are captured in the HbA_{1c} and fasting C-peptide, which likely reflect a conglomerate of other clinical variables that predispose to diabetes.

In a separate analysis, we observed that islet mass transplanted was strongly predictive of diabetes outcomes, as expected and similar to single-center studies (34). Insulin independence was uncommon under 2,500 IEQ/kg transplanted, while the majority of individuals over this threshold had islet graft function. We also noted that an islet size index consistent with more larger islets was associated with increased insulin dose required and lower C-peptide. We postulate that this is due to less hypoxia in small islets during revascularization, but it is also possible that β -cell density is different in small islets (7,36).

While timing of TPIAT is largely dictated by pain symptoms, balancing surgical risks with likelihood of diabetes

burden is an important consideration for providers and patients. Data from our study will be valuable in counseling patients on their specific risks for insulin dependence or islet graft failure after TPIAT. In addition, our data support intervening earlier in a patient who is likely to progress to TPIAT to optimize diabetes outcomes. Over time, patients undergoing TPIAT may benefit from current or emerging technologies to improve diabetes control, including automated pump systems and future stem-cell-derived islet therapies (37,38). Notably, we did see occurrence of severe hypoglycemia in this cohort, which may also benefit from newer diabetes technologies, though hypoglycemia was observed even in insulin-independent TPIAT, similar to prior reports, and may relate to the surgical alterations in intestinal anatomy (39).

To our knowledge, this is the largest prospective study conducted in TPIAT across multiple centers, with standardized collection protocols across centers for preoperative predictors and postoperative outcomes. However, individuals who were enrolled in POST were already considered to be clinically good candidates for TPIAT, potentially limiting our power to detect certain variables that predict poor or good outcomes. For example, alcoholic pancreatitis has previously been associated with worse diabetes outcomes, but alcoholic pancreatitis was rare in our cohort (40). While other studies have looked at some of the same predictors we studied, the originality of our work is in the multicenter and standardized approach implemented for prospective data collection. Stimulated islet functional testing was not obtained as part of this study due to challenges in conducting such testing across all sites, introducing some limitations in assessing islet function post-TPIAT based on fasting C-peptide alone.

We did not have the benefit of a transplant-alone control group to further elucidate the benefits of islet autotransplantation versus no islets at all, but we know that the latter would have absent islet function and are reported in the literature as more challenging to achieve stable glucose control (41). Furthermore, our findings were limited by some missing data. Despite nearly 95% retention of our cohort, not all participants followed up with recommended clinical laboratory testing, so analyses

for glycemic control and islet function are based on available data. However, findings were relatively consistent, even out to later time points of 2–4 years, strengthening the validity of these data.

In conclusion, in this multicenter study of outcomes after TPIAT, most patients had islet graft function, with nearly 20% off insulin at 1 year post-TPIAT. Lower HbA_{1c} and higher fasting C-peptide before TPIAT were associated with more favorable outcomes, and children generally had superior islet function outcomes compared with adult TPIAT recipients. These data support the value of offering islet autotransplantation at the time of transplant for pancreatitis, especially for individuals who do not have pancreatic diabetes before pancreatectomy.

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