Predictors of Glycemic Outcomes at 1 Year Following Pediatric Total Pancreatectomy With Islet Autotransplantation

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OBJECTIVE

Total pancreatectomy with islet autotransplantation (TPIAT) is indicated to alleviate debilitating pancreas-related pain and mitigate diabetes in patients with acute recurrent and chronic pancreatitis when medical/endoscopic therapies fail. Our aim was to evaluate predictors of insulin requirement at 1 year following TPIAT in a cohort of children.

RESEARCH DESIGN AND METHODS

This was a review of 43 pediatric patients followed after TPIAT for 1 year or longer. Primary outcome was insulin use at 1 year, categorized as follows: insulin independent, low insulin requirement (<0.5 units/kg/day), or high insulin requirement (≥0.5 units/kg/day).

RESULTS

At 1 year after TPIAT, 12 of 41 (29%) patients were insulin independent and 21 of 41 (51%) had low and 8 of 41 (20%) had high insulin requirement. Insulin-independent patients were younger than those with low and high insulin requirement (median age 8.2 vs. 14.6 vs. 13.1 years, respectively; *P* = 0.03). Patients with insulin independence had a higher number of transplanted islet equivalents (IEQ) per kilogram body weight (*P* = 0.03) and smaller body surface area (*P* = 0.02), compared with those with insulin dependence. Preoperative exocrine insufficiency was associated with high insulin requirement (*P* = 0.03). Higher peak C-peptide measured by stimulated mixed-meal tolerance testing (MMTT) at 3 and 6 months post-TPIAT was predictive of lower insulin requirement at 1 year (*P* = 0.006 and 0.03, respectively).

CONCLUSIONS

We conclude that insulin independence following pediatric TPIAT is multifactorial and associated with younger age, higher IEQ per kilogram body weight transplanted, and smaller body surface area at time of operation. Higher peak C-peptide measured by MMTT following TPIAT confers a higher likelihood of low insulin requirement.

Chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP) cause significant burden for pediatric patients. Pediatric pancreatitis has become more widely recognized over the past two decades and adversely impacts quality of life outcomes to

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a similar degree as in adults (1). Over time, CP constitutes an inflammatory process that causes irreversible damage to the pancreatic parenchyma (2). Many pediatric patients with CP will become opioid dependent due to chronic pain (3). Total pancreatectomy with islet autotransplantation (TPIAT) is aimed at alleviating intractable pain and debilitation caused by CP/ARP when traditional medical and procedural methods have failed to adequately improve symptoms and stop progression of disease. The operation has been shown to allow the majority of children to discontinue opioid medications and improve their quality of life (4,5). The islet autotransplantation component is intended to mitigate a brittle form of diabetes that develops with total pancreatectomy. Adult studies have shown that nearly one-third of patients are insulin independent at 1 year after surgery and the strongest predictors of insulin independence are preoperative glycemic status and islet yield (6–8). Less is known about glycemic outcomes after TPIAT in pediatric patients. Previous evidence in a pediatric cohort has shown that younger age at the time of operation, smaller body surface area, and higher islet count transplanted confer a greater likelihood of insulin independence (9). Additional pediatric studies are needed to validate these prior findings. In addition, there is a paucity of literature describing pre- and postoperative (3, 6, and 9 months) laboratory and clinical measures as predictors of glycemic outcomes and insulin requirements, which we have undertaken in this study.

Prior work in adult TPIAT populations has shown that a normal oral glucose tolerance test (OGTT) preoperatively confers a higher likelihood of becoming insulin independent after TPIAT (10). However, a mixed-meal tolerance test (MMTT) elicits a more significant C-peptide response when compared with OGTT and has been frequently used in pediatrics to assess β-cell function in patients with type 1 diabetes (11,12). MMTT is more sensitive in detecting β-cell dysfunction compared with standard OGTT and is now the test of choice for testing endocrine abnormalities in exocrine pancreatic disease like CP and pancreatic cancer, with limited data in pediatric TPIAT patients (12,13). Studies in adult TPIAT populations have shown that preoperative MMTT can predict islet yield (14). However, there has been no prior literature evaluating postoperative MMTT at different time points post–islet autotransplantation in relation to insulin requirements in TPIAT patients. The current study was conducted to evaluate clinical and laboratory predictors of glycemic outcomes and insulin requirements at 1 year after TPIAT in a pediatric cohort and to explore novel factors, both pre- and postoperative, to predict insulin requirements after TPIAT.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This institutional review board–approved single-center study was a retrospective cross-sectional analysis of a prospectively maintained patient database. We reviewed 43 patients (<20 years old) who underwent TPIAT at our center between April 2015 and January 2019. Patients who had a subtotal pancreatectomy with islet autotransplantation and patients with type 1 diabetes were excluded from this analysis. Clinical information was collected: patient demographics, etiology of disease (including genetic causes of pancreatitis), interval duration of pancreatitis, progression from first attack to CP, islet data including total islet count and islet equivalents (IEQ) per kilogram body weight, insulin requirements, growth parameters, and laboratory studies including hemoglobin A_{1c} (HbA_{1c}) and glucose, insulin, and C-peptide values collected during MMTT sampling. The primary outcome was insulin requirement at 1 year following surgery, categorized as follows: *1*) those who were insulin independent and *2*) those with low insulin requirement (<0.5 units/kg/day), and 3) those with high insulin requirement (≥0.5 units/kg/day) (15). Patients were classified as insulin independent at 1 year following surgery if they were able to maintain HbA_{1c} <7.0% off of insulin for a minimum of 14 days. Graft function was evaluated as a secondary end point by adaptation of the Igls criteria, which incorporate insulin requirements, hypoglycemic events, HbA_{1c}, and C-peptide values to assess functionality of the graft (15–17).

All potential patients with CP and ARP underwent a standardized assessment by a team of pediatric subspecialists at our institution, including a pediatric transplant surgeon, gastroenterologist, endocrinologist, pain management specialist, and a psychologist, to deem whether the patient was an appropriate candidate for TPIAT (18). CP and ARP were defined as published by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) (2). Exocrine pancreatic insufficiency (EPI) (19) was defined as stool fecal elastase level <100 μg/g or an endoscopic pancreatic function test consistent with EPI (20). Patients and families underwent thorough preoperative counseling regarding the procedure. TPIAT was performed as previously described at our institution (18).

Postoperative Care, Laboratory Studies, and Calculated Measures

All patients were admitted to the intensive care unit for a minimum of 7 days for postoperative care, including pain control and insulin and heparin infusions. Blood glucose levels were monitored with hourly blood glucometer checks with an Accu-Chek glucometer that was calibrated daily. Insulin infusion was titrated per institutional modified protocol to maintain blood glucoses in a range of 80–120 mg/dL (9). After transferring out of the intensive care unit, patients were transitioned from intravenous insulin infusion to subcutaneous insulin therapy. From 2015 to 2017, patients transitioned to subcutaneous injections before pump therapy, but after August 2017 all patients transitioned directly from intravenous insulin to subcutaneous pump therapy (21). Patients and their families received extensive education from certified diabetes educators throughout their admission. All TPIAT patients were discharged from the hospital using insulin infusion pumps and continuous glucose monitoring devices.

Patients returned at a minimum every 3 months throughout the first year after TPIAT for clinical evaluation by our multidisciplinary team. MMTT (boost 6 mL/kg, maximum dose 360 mL) were performed preoperatively and at 3, 6, and 9 months postoperatively for evaluation of islet function (11). Blood samples were obtained at times 0, 30, 60, 90, and 120 min for determination of glucose, insulin, and C-peptide values. Insulin-dependent patients were maintained on prescribed basal insulin for the duration of the test; therefore, C-peptide values were used for postoperative analysis. In addition, HbA_{1c} values were collected during these visits. Area under

the curve (AUC) over baseline for C-peptide was calculated with Riemann sums based on the midpoint of each interval for times 0, 30, 60, 90, and 120 min. HOMA of insulin resistance (HOMA-IR) was calculated: (fasting glucose * fasting insulin) / 405. HOMA of β-cell function (HOMA-β) was calculated as (fasting insulin * 360) / (fasting glucose − 63) (22). Insulinogenic index, a measure of insulin secretion in response to a glycemic load, was calculated as $\Delta insulin_{30–0\ min}/\Delta glucose_{30–0\ min}$ (23). We calculated C-peptide secretion index by replacing C-peptide in the insulinogenic index formula as a measure of C-peptide secretion ($\Delta C\text{-}peptide_{30–0\ min}$ / $\Delta glucose_{30–0\ min}$) (24). Disposition index for C-peptide, which is a ratio of insulin or C-peptide secretion to sensitivity, was calculated as follows: ($\Delta C\text{-}peptide_{30–0\ min}$ / $\Delta glucose_{30–0\ min}$) × (1 / fasting C-peptide) (25).

Statistical Analysis

Data were analyzed with SAS, version 9.4 (SAS Institute, Cary, NC). Due to skewed distributions and small sample sizes, continuous data are summarized as median with interquartile range (IQR) (25th–75th percentiles). Categorical data are summarized as frequency counts and percentages. For continuous data, Kruskal-Wallis tests were used for comparisons between insulin groups. χ^2 and Fisher exact tests were used, as appropriate, for group comparisons of categorical data. Ordinal (independent, low, high insulin) and binary (on/off insulin) logistic regression models were used to assess predictors at 3, 6, and 9 months post-TPIAT for insulin requirements at 1 year. The covariates examined in each model were age at TPIAT, BMI percentile at the particular visit, baseline BMI percentile, change in BMI percentile (from baseline to the visit time point), fasting glucose, HbA_{1c}, $AUC_{C\text{-}peptide}$, fasting C-peptide, and peak C-peptide. BMI percentile at the time of each visit and age at TPIAT were included in all logistic regression models as covariates to control for age differences and the potential influence BMI can have on metabolic measures. *P* values and Akaike information criterion were used to assess which variables were better predictors in the models. A $P < 0.05$ was considered significant.

RESULTS

Baseline Patient Characteristics

Clinical/demographic characteristics are summarized in Table 1. There were 43 patients included in the current study, with a median age at the time of TPIAT of 13.5 years (IQR 8.9–16.5). The majority (93%) of patients were diagnosed with CP. Thirty-one (72%) patients tested positive for a genetic risk factor, and *CFTR* (cystic fibrosis transmembrane conductance regulator) was the most common gene mutation (39%). Eight patients (19%) tested positive for more than one genetic risk factor, of which *CFTR* plus *SPINK1* (serine protease inhibitor Kazal type 1) was the most common combination (five of eight [62.5%]). Two patients within our cohort were diagnosed with cystic fibrosis based on genetic tests and sweat chloride testing.

Insulin Requirements at 1 Year Following TPIAT

At 1 year following TPIAT, 12 of 41 (29%) patients were insulin independent and 21 of 41 (51%) had low and 8 of 41 (20%) had high insulin requirement. At

Table 1—Patient demographics and clinical characteristics

N	43
Age at TPIAT (years)	13.5 (8.9–16.5)
Sex (female)	29 (67)
Diagnosis	
ARP	3 (7)
CP	40 (93)
BMI percentile	75.2 (49.5–93.4)
BMI >85th percentile	18 (42)
Body surface area	1.6 (1.1–1.8)
Had prior pancreatic operation	3 (7)
Number of ERCPs	3.0 (1.0–4.0)
Exocrine insufficiency	21 (51)
Endocrine insufficiency	7 (16)
Impaired fasting glucose	3 of 7 (43)
Insulin requirement	4 of 7 (57)
Prior insulin use (any duration)	4 (9)
Genetic testing positive	31 (72)
PRSS1	10 of 42 (24)
SPINK1	11 of 41 (27)
CFTR	16 of 41 (39)
CTRC	1 of 37 (3)
CPA1	2 of 24 (8)
More than one gene affected	8 (19)
CFTR + *SPINK1*	5/8 (62.5)
CFTR + *SPINK1* + *PRSS1*	1/8 (12.5)
CFTR + *CTRC*	1/8 (12.5)
CFTR + *PRSS1*	1/8 (12.5)
Number of genes affected	
Zero	12 (28)
One	23 (53)
Two	7 (16)
Three	1 (2)
Sweat chloride test (CF) (mmol/L)	
Negative	27 of 33 (82)
Indeterminate (30–60)	4 of 33 (12)
Positive (>60)	2 of 33 (6)

Data are median (25th–75th percentile) or *n* (%) unless otherwise indicated. ERCP, endoscopic retrograde cholangiopancreatography. Patients were defined as having impaired fasting glucose if the fasting blood glucose was >100 mg/dL. Patients with any insulin requirement at the time of TPIAT were included in the endocrine insufficiency group.

the end of follow-up, 15 of 41 (37%) patients remain insulin independent, with a median follow-up time of 2.4 years from surgery (IQR 1.6–3.4). Data at 1 year were unavailable for two patients, as both were lost to follow-up.

Perioperative Markers of Insulin Requirements

The insulin-independent patients were younger at presentation than those with low and high insulin requirement (8.2 vs. 14.6 vs. 13.1 years old, respectively; P = 0.03) (Table 2). Insulin-independent patients also had a lower body surface area than those with low or high insulin requirement (P = 0.02). EPI was associated with high insulin requirement (P = 0.03). Patients with insulin independence had a higher number of transplanted IEQ per kilogram body weight compared with those with insulin dependence (P = 0.03). The majority of patients had islets infused into the liver; however, in seven patients islets were infused into the peritoneal cavity. In six patients this was due to elevated portal pressure and in one patient due to liver disease. There was no statistical difference found between infusion site and insulin outcomes at 1 year (P = 0.41). From preoperative metabolic studies, HOMA-IR was significantly higher in those with high insulin requirement at 1 year (P = 0.02). $AUC_{C\text{-peptide}}$ as calculated from all time points during MMTT (0, 30, 60, 90, and 120 min) was

Table 2—Clinical factors pre-TPIAT

	Off insulin	<0.5 TDD/kg	≥0.5 TDD/kg	*P*
N (%)	12 (29)	21 (51)	8 (20)	
TPIAT age (years)	8.2 (4.7–13.1)	14.6 (12.6–16.6)	13.1 (11.3–16.1)	**0.03**
Sex (female)	9 (75)	13 (62)	6 (75)	0.74
Diagnosis				1.00
ARP	1 (8)	2 (10)	0 (0)	
CP	11 (92)	19 (90)	8 (100)	
IEQ/kg body wt	9,739 (6,160–12,500)	6,120 (3,992–6,611)	5,044 (4,212–7,133)	**0.03**
BMI percentile	68.3 (46.4–74.2)	84.0 (54.2–92.9)	89.4 (74.1–96.7)	0.31
BMI >85th percentile	2 (17)	10 (48)	5 (63)	0.09
Weight percentile	46.5 (35.0–58.4)	74.1 (49.6–87.2)	93.5 (64.4–98.2)	**0.04**
Height percentile	20.6 (14.3–39.1)	48.8 (23.4–75.1)	80.2 (63.4–90.2)	**0.02**
Body surface area	0.9 (0.7–1.5)	1.6 (1.4–1.8)	1.7 (1.4–2.0)	**0.02**
Duration between 1st AP attack and operation (years)	1.6 (1.3–2.7)	2.8 (1.9–6.8)	2.7 (1.1–6.1)	0.32
Duration between CP and operation (years)	0.8 (0.5–1.9), *n* = 11	1.8 (1.0–3.5), *n* = 19	1.5 (0.5–3.6)	0.29
Number of AP attacks total	6.0 (4.5–9.5)	8.0 (6.0–11.0)	11.0 (6.0–14.5)	0.20
Had prior pancreatic operation	1 (8)	1 (5)	1 (13)	0.76
Number of ERCPs	3.0 (1.5–3.0)	3.0 (2.0–4.0)	1.5 (1.0–2.5)	0.30
Exocrine insufficiency	7 (58)	6 of 19 (32)	7 (88)	**0.03**
Endocrine insufficiency (impaired fasting glucose or insulin requirement)	1 (8)	3 (15)	3 (38)	0.29
Prior insulin use	0 (0)	1 (5)	3 (38)	**0.02**
Genetic testing positive	11 (92)	15 (71)	4 (50)	0.14
PRSS1	4 (33)	4 of 20 (20)	1 (13)	0.61
SPINK1	3 of 11 (27)	6 of 20 (30)	2 (25)	1.00
CFTR	7 of 11 (64)	7 of 20 (35)	2 (25)	0.24
CTRC	0 of 11 (0)	1 of 17 (6)	0 of 7 (0)	1.00
CPA1	1 of 8 (13)	1 of 11 (9)	0 of 4 (0)	1.00
More than one gene affected	4 (33)	3 (14)	1 (13)	0.50
Number of genes affected				0.27
Zero	1 (8)	6 (29)	4 (50)	
One	7 (58)	12 (57)	3 (37.5)	
Two	4 (33)	2 (10)	1 (12.5)	
Three	0 (0)	1 (5)	0 (0)	
Sweat chloride test (CF) (mmol/L)				0.90
Negative	7 of 10 (70)	11 of 13 (85)	7 (87.5)	
Indeterminate (30–60)	2 of 10 (20)	1 of 13 (8)	1 (12.5)	
Positive (>60)	1 of 10 (10)	1 of 13 (8)	0 (0)	

Insulin groupings at 1 year after TPIAT. Data are presented as median (25th–75th percentile) or *n* (%) unless otherwise indicated. AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; TDD, total daily dose. *P* values in boldface are statistically significant.

Table 3—Pre-TPIAT metabolic markers (no prior insulin use *n* = 37)

	Off insulin	<0.5 TDD/kg	≥0.5 TDD/kg	*P*
N	12	20	5	
HbA_{1c} (%)	5.1 (5.0–5.4)	5.1 (4.9–5.3), *n* = 19	4.7 (4.7–5.1)	0.38
HbA_{1c} (mmol/mol)	32 (31–36)	32 (30–34)	28 (28–32)	
Fasting glucose (mg/dL)	86.5 (84.0–90.0), *n* = 10	90.5 (85.0–94.0), *n* = 18	90.0 (85.5–94.0), *n* = 4	0.60
Fasting C-peptide (ng/mL)	0.8 (0.6–1.7), *n* = 10	1.5 (1.0–1.9), *n* = 18	1.8 (1.0–2.3)	0.18
Peak C-peptide (ng/mL)	3.3 (2.1–5.3), *n* = 10	5.6 (4.0–7.5), *n* = 18	7.6 (3.6–11.4)	0.07
$AUC_{C\text{-peptide}}$	253.5 (202.5–384.0), *n* = 9	502.5 (337.5–597.0), *n* = 17	665.3 (438.0–876.0), *n* = 4	**0.04**
HOMA-IR (fasting)	0.8 (0.6–1.3), *n* = 10	1.5 (0.9–2.2), *n* = 18	2.9 (1.4–4.2), *n* = 4	**0.03**
HOMA-β (fasting)	47.2 (36.0–82.3), *n* = 10	85.5 (66.0–137.0), *n* = 18	182.9 (73.5–326.7), *n* = 4	0.07
Insulinogenic index	1.0 (0.7–2.6), *n* = 9	2.0 (0.7–3.7), *n* = 16	2.3 (1.1–4.4), *n* = 4	0.81
C-peptide secretion index	0.11 (0.07–0.26), *n* = 9	0.12 (0.06–0.17), *n* = 16	0.14 (0.07–0.20), *n* = 4	0.96
Disposition index: C-peptide	0.12 (0.08–0.43), *n* = 9	0.07 (0.05–0.10), *n* = 16	0.07 (0.03–0.10), *n* = 4	0.14
Proinsulin	1.1 (1.1–1.8), *n* = 5	2.2 (2.0–4.1), *n* = 5	6.9 (1.1–12.6), *n* = 2	0.45

Data are median (25th–75th percentile) or *n* (%) unless otherwise indicated. Four patients on insulin pre-TPIAT were excluded. HOMA-IR = (fasting glucose * fasting insulin) / 405. HOMA-β = (fasting insulin * 360) / (fasting glucose − 63). C-peptide secretion index = $\Delta C\text{-peptide}_{30\text{–}0\ min}$ / $\Delta glucose_{30\text{–}0\ min}$. Insulinogenic index = $\Delta insulin_{30\text{–}0\ min}$ /$\Delta glucose_{30\text{–}0\ min}$. Disposition index: C-peptide = $\Delta C\text{-peptide}_{30\text{–}0\ min}$ /$\Delta glucose_{30\text{–}0\ min}$ × 1 / fasting C-peptide. TDD, total daily dose. *P* values in boldface are statistically significant.

also significantly higher pre-TPIAT in those with high insulin requirement at 1 year (*P* = 0.04) (Table 3). There was no difference in preoperative fasting glucose or HbA_{1c} values between insulin groups at 1 year.

Postoperative Markers of Insulin Requirements

MMTT were evaluated at 3, 6, and 9 months following TPIAT for prediction of insulin outcomes. BMI percentile at the time of each visit and age at TPIAT were included in the model. In evaluations of insulin outcome at 1 year defined as off insulin and low and high insulin requirement, higher stimulated peak C-peptide from MMTT was significantly associated with lower insulin requirement at 3 and 6 months (*P* = 0.006 and 0.03, respectively) (Supplementary Table 1) and there was a trend toward significance at 9 months (*P* = 0.056). (See Supplementary Fig. 1 for peak C-peptide values for the time points.) In evaluating insulin outcome at 1 year as defined as on or off insulin, higher stimulated peak C-peptide was significantly associated with higher likelihood of insulin independence at 3, 6, and 9 months (*P* = 0.02, 0.02, and 0.04). At 3 months, the majority of peak C-peptide values occurred at 30 or 90 min during the MMTT, and at 6 and 9 months the peak C-peptide occurred most often at 120 min. Fasting C-peptide, AUC C-peptide, and fasting glucose were also assessed. Fasting C-peptide was not statistically significant for predicting 1-year insulin outcomes for either ordinal (off insulin, low or high insulin requirement) or binary (on/off insulin). AUC C-peptide was significant for some months, but peak C-peptide was a better predictor with regard to *P* values and Akaike information criterion.

Evaluation of Graft Function

We defined our graft outcomes as adapted from the Igls criteria at 1 year following operation (15) (Table 4). There were 12 of 41 patients (29%) with optimal function, 13 of 41 (32%) with good function, 10 of 41 (24%) with marginal function, and 6 of 41 (15%) with graft failure. (See Supplementary Table 2 for graft and insulin outcomes.) Of those with marginal function, all 10 patients had HbA_{1c} >7% (53 mmol/mol) and 1 of 10 (10%) had severe hypoglycemia.

CONCLUSIONS

In our study we aimed to identify pre- and postoperative clinical and metabolic factors affecting insulin requirements and glycemic outcomes at 1 year after pediatric TPIAT. This is the first pediatric study with examination of the utility of MMTT at regular intervals pre- and postoperatively as a predictive tool for insulin requirements at 1 year postsurgery. In addition, in this study we sought to validate previously published data within the pediatric TPIAT population. Strengths

Table 4—Adapted Igls criteria for categorizing graft function

β-cell graft functional status	HbA_{1c}, %	Severe hypoglycemia	Insulin requirement	C-peptide (ng/mL)	Treatment success	*N* (%)
Optimal	≤6.5	None	None	Detected (>0.5)	Yes	12 of 41 (29%)
Good	<7.0	None	Yes	Detected (>0.5)	Yes	13 of 41 (32%)
Marginal	≥7.0	Yes	Yes	Detected (>0.5)	No	10 of 41 (24%)
Failure	—	—	—	Undetected	No	6 of 41 (15%)

of our study include the use of pre- and postoperative metabolic factors in creating a predictive model for insulin requirements at 1 year post-TPIAT and the inclusion of genetic analysis on nearly all patients. In this study, we have shown that higher HOMA-IR and $AUC_{C\text{-}peptide}$ from pre-TPIAT metabolic studies confer an increased likelihood of high insulin requirement at 1 year following operation. From postoperative metabolic studies, we demonstrated that higher values of stimulated peak C-peptide at 3, 6, and 9 months post-TPIAT were associated with low insulin requirement when controlling for BMI percentile and age at TPIAT.

Consistent with previous reports, nearly one-third of our cohort achieved insulin independence at 1 year following operation (4,7). Consistent with previously reported literature, the predictors of insulin independence at 1 year included younger age, higher transplanted IEQ per kilogram body weight, and smaller body surface area (9,26). We also found no history of prior insulin use as a predictor. Preoperative diabetes has been shown to be associated with higher insulin requirement at 1 year following operation (10), which was validated in the current study. Preoperative EPI was shown to be associated with an increased risk of high insulin requirements at 1 year following operation. Prior literature has shown that EPI is associated with a higher incidence of diabetes in adults with CP, but EPI has not been studied well as a predictor of insulin requirement post-TPIAT in pediatric patients. (27). EPI is typically associated with longer disease duration, which can concomitantly lead to fibrotic injury and destruction of islet cells (20). This finding should be validated in future studies, as nearly one-half of our patients with EPI were insulin independent at 1 year.

Metabolic studies performed before TPIAT showed higher HOMA-IR and $AUC_{C\text{-}peptide}$ in those with high insulin requirement. This finding suggests that pediatric patients with insulin resistance and higher degree of secretion of C-peptide prior to surgery tend to have a high insulin requirement following surgery. In addition, there was a trend toward significance of higher peak C-peptide values pre-TPIAT in those with high insulin requirements. This contrasts with prior adult literature, in which preoperative higher $AUC_{C\text{-}peptide}$ and peak C-peptide values correlate with improved glycemic outcomes (14). Data from the Diabetes Prevention Trial–Type 1 (DPT-1) cohort have shown that C-peptide values in childhood increase with increasing age and BMI (28). The Type 1 Diabetes TrialNet Study Group has shown a similar finding, demonstrating that there are age-related differences in C-peptide levels, with those $<$12 years having the lowest C-peptide levels and those $>$18 years having the highest levels (29). We postulate that these age- and BMI-related differences may account for our findings pre-TPIAT, as the insulin-independent patients within our cohort were younger and accounted for a smaller fraction of those with a BMI $>$85th percentile; however, these factors were controlled for in the predictive logistic regression models at the 3-, 6-, and 9-month time points. We also found no relation between preoperative HbA_{1c}, fasting glucose, fasting insulin, or C-peptide values and 1-year insulin outcomes, as the large majority of patients were normoglycemic prior to surgery. Our results indicate that presurgical fasting levels are not good predictors of islet outcomes post–pediatric TPIAT. However, fasting values have been found to be useful predictors in the allogenic transplantation population and our results would indicate further investigation of pretransplant $AUC_{C\text{-}peptide}$ and HOMA-IR values (15).

Higher values of stimulated peak C-peptide at 3, 6, and 9 months post-TPIAT were associated with lower insulin requirement when BMI percentile and age at TPIAT were controlled for. At 3 months, the majority of peak C-peptide values occurred at 30 or 90 min during the MMTT, and at 6 and 9 months the peak C-peptide occurred most often at 120 min. Fasting C-peptide and fasting glucose values were not significantly associated with insulin requirements at any time points. Peak C-peptide value was the strongest predictor of insulin outcome at each time point, which supports the use of an MMTT study rather than fasting values alone for glycemic outcome prediction. One study has shown that a fasting blood sample can be used to calculate a BETA-2 score as an estimate of β-cell function to predict insulin independence (16). In the current study, BETA-2 score was a predictor of 1-year insulin outcomes comparable with stimulated C-peptide levels; however, the authors focused on C-peptide levels given the laborious nature of calculating this score. Additionally, in the clinical setting it is easier to obtain C-peptide levels.

As demonstrated, IEQ per kilogram body weight in our study were higher than previously reported (7–9). Surprisingly, some of our patients had high transplanted IEQ per kilogram body weight but had graft failure following surgery. This is a limitation of the current study and may bring into question the accuracy of islet counts; however, there is consistency within our population. In islet preparations from two patients, the isolation index, which is calculated as the ratio of IEQ to islet number, was $<$1. Fragmentation of islets is a feasible explanation for the observed low islet size (isolation index) (30). Poor survival of fragmented islets may be the cause for primary nonfunction of transplanted islets. In another case, the cause for islet functional failure was unknown.

In recent years there has been an aim to standardize graft outcomes in relation to glycemic control in islet cell transplant recipients, which led to the creation of the Igls criteria (15). This criteria has been modified for application to the TPIAT population and incorporates HbA_{1c}, insulin requirements, C-peptide values, and events of severe hypoglycemia (16). In our population, classification by modified Igls criteria revealed that the majority (61%) of patients were in the optimal or good graft function categories. As understanding of graft function after TPIAT evolves over time, it will become more important to assess C-peptide in relation to glycemic status as the outcome of graft function rather than detectable C-peptide alone (15).

Although with this study we present the utility of MMTT in predicting insulin requirements post-TPIAT as a novel concept, the study is not without limitations. Limitations include the small sample size and single-center design, which may make our findings less generalizable. Two patients were lost to follow-up, which could have introduced selection bias. Another limitation is that the islet counts in many of our patients may be higher than previously reported in other cohort studies. However, there is consistency in the method applied to count the islets within our own population with use of the same islet facility, and this

finding does not impact the glycemic outcomes reported in our study.

Conclusion

At 1 year following TPIAT, insulin-independent patients in our cohort were younger at time of TPIAT, had smaller body surface area at the time of TPIAT, had no history of prior insulin use, and had higher IEQ per kilogram body weight transplanted. Patients with preoperative lower $AUC_{C\text{-peptide}}$ and HOMA-IR had lower insulin requirements following TPIAT. Higher stimulated peak C-peptide at 3 and 6 months post-TPIAT was a significant predictor of insulin independence and low insulin requirement when BMI percentile and age at TPIAT were controlled for. The majority (61%) of patients had optimal or good graft function based on modified Igls criteria. Future studies are needed to focus on validating these findings on a larger scale, with multicenter cohort designs to further define predictors of islet graft function and insulin requirements post-TPIAT.

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