Age and Disease Duration Impact Outcomes of Total Pancreatectomy and Islet Autotransplant for *PRSS1* Hereditary Pancreatitis

Melena D. Bellin, MD, MS,†‡ Polina Prokhoda,† James S. Hodges, PhD,§ Sarah J. Schwarzenberg, MD,* Martin L. Freeman, MD,|| Ty B. Dunn, MD,† Joshua J. Wilhelm, MS,‡ Timothy L. Pruett, MD,† Varvara A. Kirchner, MD,† Gregory J. Beilman, MD,† and Srinath Chinnakotla, MD*†*

Objectives: We investigated the impact of patient age and disease duration on islet isolation results, diabetes outcomes, and pain outcomes after total pancreatectomy with islet autotransplant (TPIAT) performed in 64 patients with hereditary pancreatitis due to *PRSS1* gene mutation.

Methods: We evaluated the association of patient age and disease duration on islet isolation results and opioid use at 1 year using logistic regression and on graft function using 1-way analysis of variance.

Results: Islet mass was negatively associated with increasing age and longer disease duration, with a 13% reduction (95% confidence interval [CI], 3%–22%) and 22% (95% CI, 14%–29%) reduction in islet equivalents per kilogram body weight (IEQ/kg) for each 5 years of age and disease duration, respectively. Full graft function was associated with younger age and shorter duration of disease ($P < 0.01$). Persistent opioid use (15% of patients at 1 year) increased with age ($P = 0.05$) and disease duration ($P = 0.04$).

Conclusions: The TPIAT outcomes were adversely impacted by older age and prolonged disease. In particular, islet mass is lower and risk of diabetes high in older patients with prolonged disease. This should be considered when counseling this subgroup of TPIAT recipients on expected outcomes.

Key Words: total pancreatectomy, chronic pancreatitis, acute pancreatitis, diabetes, hereditary pancreatitis, *PRSS1*

Abbreviations: TPIAT - total pancreatectomy with islet autotransplant, *PRSS1* - protease serine 1, HbA1c - hemoglobin A1c, IN - islet number, IN/kg - islet number per kilogram body weight, IEQ - islet equivalents, IEQ/kg - islet equivalents per kilogram body weight, SF-36 - Short Form-36, MCS - mental component summary score, PCS - physical component summary score

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Chronic pancreatitis is an inflammatory condition of the pancreas that causes pain and progressive damage to the exocrine and endocrine pancreatic tissue.[1] One cause of chronic pancreatitis is autosomal dominant hereditary pancreatitis, due to a mutation in the gene encoding cationic trypsinogen (protease serine 1, or *PRSS1*), mapped to the 7q35 region of the long arm of human chromosome 7.[2–4] Pathogenic mutations in the *PRSS1* gene convey more than an 80% chance for recurrent acute and/or chronic pancreatitis, as well as exceptionally high lifetime risk (estimated at 40%) for pancreatic ductal adenocarcinoma.[4,5]

When pancreatitis results in severe pain or disability and is nonresponsive to medical or endoscopic treatment, total pancreatectomy with islet autotransplantation (TPIAT) may be considered.[6] Considerations specific to the *PRSS1* population, distinct from the general TPIAT population, include a typically young age at first symptoms (often <10 years) and higher lifetime risk for pancreatic cancer.[7,8]

Among all TPIAT recipients, regardless of cause of pancreatitis, we have previously reported improved quality of life. Although opioid use is significantly reduced, approximately 40% continue to require opioids over the first 1 to 2 years after the operation.[9] Insulin independence after surgery occurs in one third of patients, with most remaining on some supplemental insulin, while having partial islet graft function.[9] We have previously compared all genetic-mediated pancreatitis with nongenetic causes and found greater prevalence for discontinuation of opioids but higher insulin dependence rate in those with genetic disease.[10] Naziruddin et al[11] recently found a very strong negative correlation between duration of disease and islet yield in 10 patients with genetic causes of pancreatitis, suggesting that diabetes outcomes may be particularly adversely impacted by prolonged disease in those with a genetic etiology.

Based on these findings and our clinical observations that older teens and adults with *PRSS1* mutations rarely achieve insulin independence, we sought to specifically evaluate the impact on outcomes of disease duration and age at which the surgery is done, in patients with *PRSS1*-mediated chronic pancreatitis undergoing TPIAT. Because pancreatic inflammation and fibrosis from *PRSS1* often start early in childhood and disease manifestations are often seen over decades,[5,8] we postulated that older age and prolonged duration of disease would present a very high risk for low islet mass and diabetes. Relating the impact of age and duration of disease in this subcohort is particularly important for providing accurate preoperative counseling of TPIAT recipients on expected outcomes and for guiding decisions about timing of the intervention in early onset hereditary pancreatitis.

MATERIALS AND METHODS

Subjects

We reviewed all patients undergoing total or complete pancreatectomy with islet autotransplant at the University of Minnesota and identified 64 patients with *PRSS1* gene mutations who underwent TPIAT between October 1, 2004, and June 26, 2015.

From the *Department of Pediatrics, †Department of Surgery, ‡Schulze Diabetes Institute, §School of Public Health, Division of Biostatistics, and ||Department of Medicine, University of Minnesota Medical School, Minneapolis, MN.

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Address correspondence to: Melena D. Bellin, MD, Room MB 671, East Bldg, University of Minnesota Masonic Children's Hospital, 2450 Riverside Ave S, Minneapolis, MN 55454 (e-mail: bell0130@umn.edu).

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All patients were participants in 1 of 2 institutional review board–approved studies; before 2006, patients were enrolled in a retrospective study with follow-up information collected by patient questionnaires and medical records review. Since 2006, all patients have been participants in a prospective observational study collecting laboratory, medical records, and patient questionnaire data at predefined intervals of 3 months, 6 months, 1 year, then yearly after TPIAT. Informed parental consent and assent or informed consent, as age appropriate, was obtained for all participants.

Total Pancreatectomy Procedure

Total pancreatectomy was performed as previously described.[12] Briefly, the entire pancreas was resected with splenectomy and partial duodenectomy, with care to preserve blood flow to the pancreas for as long as possible to reduce warm ischemia time. Gastrointestinal continuity was restored by duodenoduodenostomy and choledochoduodenostomy in early cases, or later with Roux-en-Y duodenojejunostomy and choledochojejunostomy.

Islet Isolation and Infusion

Islet isolation was performed as previously described.[9] Briefly, the pancreas was distended with a collagenase and neutral protease solution. The enzyme preparations used have varied over time and are divided into 3 enzyme eras for analysis: era 1: Roche Liberase HI (Roche CustomBiotech, Indianapolis, Ind); era 2: SERVA collagenase and SERVA neutral protease (SERVA, Heidelberg, Germany); and era 3: VitaCyte intact C1 collagenase (VitaCyte, Indianapolis, Ind) and SERVA neutral protease (SERVA, Heidelberg, Germany). Subsequently, the pancreas was mechanically disrupted using the semiautomated method of Ricordi. COBE 2991 cell processor (Terumo BCT, Lakewood, Colo) purification was undertaken only when digest tissue volume exceeded 0.25 mL/kg body weight.[13] The final islet tissue preparation was suspended in 200 mL CMRL culture medium (Mediatech, Inc, Manassas, Va) per infusion bag. Heparin was added to the bag and/or administered to the recipient at a total of 70 unit/kg body weight, with heparin or enoxaparin continued for 1 week postoperatively to prevent portal vein thrombosis.[14]

Collection of End Point Data

Medical records and data abstracted for pain medication use, insulin requirements, and laboratory measures including hemoglobin (HbA1c), fasting glucose and C-peptide, and stimulated glucose and C-peptide during a mixed meal tolerance test (6 mL/kg of Boost HP, with glucose and C-peptide at 60 and 120 minutes) were reviewed.

Patient questionnaires were administered at 3 months, 6 months, and yearly after TPIAT for participants undergoing surgery since 2006. These included questions on pain medication use, pain scores, diabetes management, insulin dosing, and health-related quality of life (RAND Short Form-36, SF-36).

Statistics

Multiple linear regression, adjusted for enzyme era (defined above), was used to estimate and test the association of disease duration and, separately, age at TPIAT with all outcomes except graft function and opioid use. To estimate and test the association of graft function with disease duration and age at TPIAT, 1-way analysis of variance was used with graft function defining the groups (failure vs partial function vs full function) and either age or disease duration as the outcome. To estimate and test the association of opioid use with disease duration or age at TPIAT, logistic regression was used with opioid use as the outcome. All analyses were done using JMP (v. 12 Pro, SAS Institute Inc, Cary, NC).

RESULTS

Demographic Characteristics

Sixty-four patients with hereditary pancreatitis secondary to *PRSS1* mutation underwent TPIAT at ages 3 to 56 years (average, 16.8 years; standard deviation [SD], 9.8 years), most patients were 40 years or younger, with exception of 2 patients aged 41 and 56 years. Average duration of diagnosed pancreatitis (SD) was 8.3 (7.3) years. Ten patients (15%) had a surgical intervention before TPIAT that did not produce sustained pain relief. Table 1 shows islet isolation characteristics and outcomes.

Longer Duration of Disease and Older Age Are Associated With a Lower Islet Mass Transplanted

For this analysis, transplanted islets were quantified as (1) islet number (IN), which is the number of islets transplanted without adjustment for islet size, and (2) islet equivalents (IEQ), a measure of islet mass in which counts are adjusted for islet volume so that large islets are weighted more heavily than small islets (ie, one islet equivalent is equal to one medium size islet with a diameter of 150 microns).

TABLE 1. Demographic Characteristics and 1-Year Outcomes for 64 Patients With *PRSS1* Undergoing TPIAT

Characteristic	
Age, mean (SD), y	16.8 (9.8)
≥21, n (%)	15 (23.4)
<21, n (%)	49 (76.6)
Sex, female, n (%)	41 (64)
Duration of diagnosed pancreatitis, mean (SD), y	8.3 (7.3)
Previous pancreatic surgery, n (%)	
Drainage (lateral pancreaticojejunostomy)	8 (12.5)
Drainage + distal pancreatectomy	2 (3.1)
Baseline average daily pain score (10-point scale, n = 45), mean (SD)	4.13 (2.44)
Baseline SF-36: MCS Score (n = 49), mean (SD)	34.4 (12.4)
Baseline SF-36: PCS Score (n = 49), mean (SD)	37.5 (11.9)
Total islets transplanted, mean (SD)	191,102 (120,122)
Total IEQ transplanted, mean (SD)	177,526 (132,210)
Islets/kg transplanted, mean (SD)	4131 (3143)
IEQ/kg transplanted, mean (SD)	3798 (2967)
1-yr outcomes	
Not using opioids, n (%)	48 (of 57 with data) (85)
Average daily pain score (n = 34), mean (SD)	1.47 (1.74)
SF-36: MCS (n = 37), mean (SD)	49.6 (9.9)
SF-36: PCS (n = 37), mean (SD)	52.2 (9.1)
Insulin independent, n (%)	18 (28.1)
Graft failure, n (%)	10 (15.6)
Hemoglobin A1c level (%), mean (SD)	6.87 (1.55)
Fasting glucose, mean (SD), mg/dL	119 (45)
Fasting C-peptide, mean (SD), ng/mL	0.86 (0.52)
Stimulated C-peptide, mean (SD), ng/mL	2.30 (1.38)

SF-36, short form 36.

MCS is normalized to healthy population mean score of 50 (SD, 10); PCS is normalized to healthy population mean score of 50 (SD, 10).

Because islet isolation yield was significantly lower in the earliest enzyme era (era 1, n = 4 patients, $P = 0.02$), analyses for association between islet isolation results with age or duration of disease were adjusted for the enzyme era. Adjusting for enzyme era, IN per kilogram body weight (IN/kg) and IEQ per kilogram body weight (IEQ/kg) were negatively associated with age ($P = 0.01$ for both) and longer duration of disease was associated with lower total IN, total IEQ, IN/kg, and IEQ/kg ($P < 0.001$ for all; Table 2). For example, this translated into a 16% reduction in IEQ and 22% reduction in IEQ/kg for every 5 years of diagnosed disease.

Risk for Diabetes After TPIAT Increases With Age and Longer Duration of Disease in *PRSS1* Hereditary Pancreatitis

Patients were classified as having full islet graft function (insulin independent), partial islet graft function, or islet graft failure at 1 and 2 years after their TPIAT procedure. Graft function at 1 year post-TPIAT was associated with age ($P = 0.004$) and duration of disease ($P = 0.008$), with full graft function more likely in those patients who were younger or had a shorter duration of disease at time of TPIAT (Fig. 1A). A similar pattern was seen at 2 years and remained significant (Fig. 1B). In fact, all patients with full graft function were both younger than 21 years and had duration of disease less than 17 years.

Comparing patients who were insulin independent versus dependent at 1 year, the insulin-independent group had shorter disease duration (mean ± standard error [SE]) (7.0 ± 2.3 vs 12.8 ± 1.4 years, $P = 0.04$) and younger age at surgery (10.1 ± 2.2 vs 18.9 ± 1.3 years, $P = 0.0012$). Peak stimulated C-peptide from MMTT at 1 year post-TPIAT (n = 44 patients) was negatively associated with duration of disease ($P = 0.026$; average change per 5 additional years disease duration, −0.28; 95% confidence interval [CI], −0.04 to −0.53) but was not associated with age at TPIAT ($P = 0.53$). There was a nonsignificant trend toward higher hemoglobin A1c level at 1 year with increasing duration of disease ($P = 0.07$; average change per 5 additional years disease duration, 0.20; 95% CI, −0.02 to 0.41).

Opioid Use Was Infrequent at 1 Year but Was Higher With Older Age and Longer Duration of Disease

Of the 57 patients with data available for pain medication requirements at 1 year post-TPIAT, only 9 (15%) required opioids. The probability of requiring opioid medications at 1 year postsurgery increased significantly with age ($P = 0.05$; odds ratio for every 5 years of age, 1.38; 95% CI, 1.00–1.90) and duration of disease ($P = 0.04$; odds ratio for every 5 years of disease duration, 1.42; 95% CI, 1.01–2.00).

Quality of Life Is Unaffected by Duration of Disease at 1 Year After Surgery but Is Negatively Associated With Age

One hundred sixteen pain and SF-36 questionnaire responses were available from 58 participants, at baseline (49 responders), 1 year (37 responders), or 2 years (30 responders). Pain scores, mental component summary score (MCSs), and physical component summary score (PCSs) generated from the SF-36 at baseline and 1 year post-TPIAT are included in Table 1. Mental component summary score and PCS were near the population normative value of 50 at follow-up. Average pain score, MCS, and PCS were not associated with duration of disease at the time of TPIAT at 1 or 2 years after surgery ($P > 0.3$ for all). However, there was a trend toward higher pain score with older age (mean ± SE) ($P = 0.07$; for every 5 years of age, 0.26 ± 0.14 points on a 10-point scale), and a modest but significant negative association between older age and PCS ($P = 0.005$; for every 5 years of age, reduced by 2.2 ± 0.80 points), and MCS ($P = 0.02$; for every 5 years of age, reduced by 1.7 ± 0.70 points) at 1 year. The latter 2 associations were largely determined by 1 outlier, the oldest patient with data. Associations between age at TPIAT and 2-year outcomes were not significant for average pain level ($P = 0.98$), PCS ($P = 0.78$), or MCS ($P = 0.80$).

DISCUSSION

Patients with *PRSS1*-mediated chronic pancreatitis are increasingly being considered for TPIAT when pain and disability are severe.[10,15] This is the most common cause for pancreatitis among children undergoing TPIAT at our center, but it is also the underlying cause of pancreatitis in an increasing number of adult TPIAT recipients. When this autosomal dominant mutation in the cationic trypsinogen gene is present, pancreatic inflammation often begins at a very young age and disease duration may be prolonged by the time surgery is considered.[5] We sought to investigate the impact of age and disease duration on pain relief and diabetes outcomes in this important subgroup of patients. We found a high rate of discontinuation of opioid use, with 85% of patients off opioids at 1 year, although the estimated probability of needing opioid therapy at 1 year increased with age. Lower islet mass and insulin dependence were common with older age and increasing duration or disease. This is an important consideration when counseling patients with *PRSS1* disease on expected outcomes after TPIAT and in considering the timing of intervention for those afflicted with severe pain from a young age.

The primary indication for TPIAT is to relieve pain and improve quality of life.[16,17] Total pancreatectomy with islet autotransplant recipients with *PRSS1* disease had benefited overall, with reduced opioid use, reduced pain scores, and improved quality of life averaging over the entire cohort. However, the probability of needing opioids at 1 year after surgery increased with age and longer disease duration. A likely explanation for this observation is that prolonged exposure to repeated painful stimuli increases the risk for central sensitization, in which pain signals continue to be inappropriately conducted in the central nervous system even after painful stimuli are removed.[18–21] Also, patients with longer disease have been exposed to repeated opioid use over an extended time period, potentially complicating opioid weaning due to opioid-induced hyperalgesia.[22] These observations are similar to those reported for pancreatic drainage surgeries in other

TABLE 2. Estimated Impact of Patient Age and Duration of Disease at Time of TPIAT on IN and Islet Mass Isolated for Transplant

	Estimated Impact of Patient Age			Estimated Impact of Duration of Disease		
	% Decrease per 5-Y Age	95% CI	*P*	% Decrease per 5-Y Disease	95% CI	*P*
IN	−0.4	−10 to 9	0.93	14	6–21	0.0007
IEQ	−0.2	−11 to 10	0.96	16	8–23	0.005
IN/kg	13	3–21	0.01	20	13–23	<0.0001
IEQ/kg	13	3–22	0.01	22	14–29	<0.0001

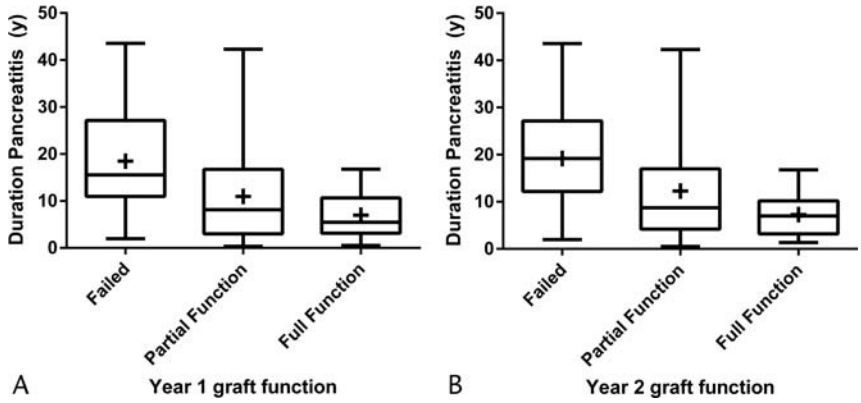

FIGURE 1. Graft function at 1 year (A) and 2 years (B) after TPIAT, based on duration of diagnosed pancreatitis before TPIAT. Box plots indicate median, 25th to 75th percentile, whiskers indicate minimum and maximum, and plus sign indicates mean.

chronic pancreatitis populations, where shorter duration of pain predicts better pain resolution.[23]

We also observed a strong association between disease duration and the diabetes outcomes. In a previous study comparing patients with any hereditary-genetic etiology of pancreatitis with those patients with no known genetic risk factors, we found a smaller and more fibrotic pancreas, lower islet mass, and lower probability of ever achieving insulin independence in those with genetic disease compared to nongenetic disease.[10] We have also previously observed that pancreatic calcifications on imaging, often a marker of prolonged disease, convey a 4-fold increased risk of diabetes.[24] Building on these previous studies, in this analysis we found specifically that those patients with *PRSS1*-mediated genetic disease who were older and had disease longer were more likely to have lower islet mass isolated and to remain on insulin therapy after surgery. The decision to intervene surgically is based on the need to intervene to reduce intractable pain or disability. However, diabetes is an important component of surgical counseling. We generally counsel *adult* patients to expect a 1 of 3 chance of insulin independence based on literature for the entire adult TPIAT population.[9] Based on the data presented here, this may give adult patients with *PRSS1* and a long disease duration unrealistic expectations for their diabetes outcomes. Patients older than 21 years or with more than 17 years of disease did not achieve insulin independence in our study, even though many of these recipients have partial islet graft function. Our population was, however, able to maintain adequate glycemic control even when insulin therapy was required. Thus, the rationale for islet autotransplant in those who are older or with a very long disease duration would be to preserve enough beta cell mass to enable the patient to more easily and safely meet the HbA1c goals of diabetes therapy while avoiding glycemic lability, which is "brittle" diabetes.

This study suggests that strategies to improve diabetes outcomes should be a consideration in this patient population. Adults or those with long disease duration had lower islet yields. However, as many as half of the islet mass infused may be lost because of the stress of islet isolation, acute inflammatory blood mediated response at the time of islet infusion, and posttransplant beta cell apoptosis.[25–27] Thus, therapies that prevent peritransplant islet loss because of these stressors may be particularly pertinent to this "high risk" population where the infused islet mass is low.[28,29]

Notably, we used the pancreatitis diagnosis date to calculate duration of disease in this population. Some patients are diagnosed late or may have subclinical disease before diagnosis so that this calculation may underestimate the true disease duration. However, this is not likely to affect our study's main finding, that very long disease duration was associated with low islet mass and lack of insulin independence. Findings for health-related quality of life suggest an overall benefit but potentially with older TPIAT recipients having worse PCS, MCS, and pain levels at 1 year. However, these data are limited by missing measures (patients treated before study surveys were administered, or nonreturn of study questionnaires). These findings should be considered in the context of these limitations.

In conclusion, patients with *PRSS1*-mediated hereditary pancreatitis benefited in terms of reduced opioid use, reduced pain symptoms, and improved health-related quality of life measures after TPIAT. Opioid use was higher, and MCS and PCS were lower at 1 year after surgery with increasing age, although most of the cohort (85%) stopped opioids by 1 year. Age greater than 21 years or disease duration longer than 17 years at surgery resulted in insulin dependence after TPIAT, with or without partial islet function. When justified by severe pain symptoms, earlier age at surgery may improve diabetes outcomes after TPIAT.

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