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Gastrointestinal Symptoms Before and After Total Pancreatectomy With Islet Autotransplantation: The Role of Pancreatic Enzyme Dosing and Adherence

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Abstract

Objectives—In a large cohort of subjects undergoing total pancreatectomy with islet autotransplantation (TPIAT), we assessed the prevalence and duration of gastrointestinal symptoms before and after the procedure and to determine the impact of enzyme adherence on gastrointestinal symptoms.

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Methods—356 pre- and post-operative questionnaires were collected from 184 subjects between ages of 5 and 66 years who underwent TPIAT between 2008 and 2011 at University of Minnesota. Questionnaires were analyzed for self-reported frequency and severity of gastrointestinal symptoms, pancreatic enzyme usage, and glycemic variability index (GVI).

Results—After surgery, patient-reported steatorrhea increased; constipation decreased. Gastrointestinal symptoms interfered with daily activity in 44–69% of subjects, before and after surgery, despite high reported enzyme adherence. Post-operatively, 79% of subjects reported consistent use of enzymes at all meals. Presence of gastrointestinal symptoms did not vary with adherence. GVI of 2 had a 2.8 fold increased odds of steatorrhea (95% confidence interval 1.1–7.0) compared to GVI of 0.

Conclusions—Gastrointestinal symptoms were common after TPIAT; ongoing management is needed. Enzyme non-adherence was not a major contributor to diarrhea/steatorrhea in this cohort. Glycemic variability was closely associated with steatorrhea; poor response to enzyme replacement may complicate diabetes management.

Keywords

Pancreatectomy; Transplantation; Autologous; Exocrine Pancreatic Insufficiency; Pancreatitis; Chronic

Introduction

Chronic pancreatitis (CP) is characterized by progressive loss of pancreatic parenchymal tissue leading to failure of pancreatic exocrine and endocrine function [1,2]. Effective treatment for this condition, which is often associated with severe pain, is limited. Since 1977, the University of Minnesota has performed over 500 total pancreatectomies with islet autotransplantation (TPIAT) on adults and children. A recent case series reported complete insulin independence or low insulin needs in 63% of patients at 3 year follow-up. Pain was improved in 85% of adults and 94% of children [3].

Until now, clinical research in this field has focused primarily on the impact of TPIAT on resolution of pain and diabetes prevention. Little has been reported on the prevalence and severity of post-operative gastrointestinal complications, including exocrine insufficiency. Gastrointestinal complications may include abdominal cramps, bloating, flatulence, steatorrhea, malnutrition, and weight loss [4,5]. In addition to putting patients at risk for fat-soluble vitamin deficiencies and resultant increases in morbidity, these symptoms may significantly interfere with daily activities and disrupt perceived quality of life. Exocrine pancreatic insufficiency is currently treated with oral exogenous enzyme replacement [5–12]. Symptoms of malabsorption result when enzyme dosing is inadequate or adherence is poor, however, other complications may produce similar symptoms, for example, small bowel bacterial overgrowth.

Herein we report, in a large prospective cohort study of adult and pediatric TPIAT patients, outcomes related to pancreatic enzyme replacement therapy (PERT), including: the prevalence and duration of GI symptoms before and after TPIAT, trends in enzyme dosing regimens, patient adherence to enzyme therapy, and treatment response.

Materials and Methods

Subjects

One hundred eighty-four patients who underwent TPIAT for chronic pancreatitis between 2006– 2011 at the University of Minnesota were enrolled in this prospective study. The surgical procedure for TPIAT and islet isolation were performed as previously described [3]. Selection criteria for TPIAT have evolved over the years. Currently, the criteria include abdominal pain of >6 mo duration with impact on quality of life, failure to respond to maximal medical or endoscopic treatment, and at least one of the following: pancreas calcifications on imaging, abnormal ERCP, or 6 of 9 criteria on endoscopic ultrasound. In addition, candidates must have 2 or 3 of the following: ductal or parenchymal abnormalities on secretin-stimulated magnetic resonance cholangiopancreatography, endoscopic ultrasound with 4 of 9 criteria positive, abnormal endoscopic pancreatic function testing, histopathologic confirmed diagnosis of CP, PRSS1 gene mutation with compatible clinical history, or history of recurrent pancreatitis with >3 episodes of pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase 3 times normal (3). Post-operative PERT dose was prescribed by the surgeon performing the procedure for adults (GB, TD) and by the pediatric gastroenterologist for children (SJS). After subjects returned home, the responsibility for PERT dosing was transitioned to the referring physician. Written informed consent was obtained from all study subjects. The study protocol was approved by the University of Minnesota Institutional Review Board.

Assessments

Health questionnaires were administered before surgery, at 3 months, 6 months, and yearly after surgery. Three hundred fifty-six patient-completed health questionnaires collected over a 3 year interval (11/1/2008– 10/31/2011) were included in this analysis. The number of completed questions at each time point that included the gastrointestinal function endpoints were as follows: 103 before surgery, 50 at 3 months, 49 at 6 months, 59 at 1 year, 49 at 2 years, and 46 at 3 years.

The health questionnaire collected demographic information along with self-reported heights and weights, current pancreatic enzyme dose, and frequency of enzyme administration. Subjects were asked to report their adherence to enzyme therapy (defined as taking prescribed dosage with every meal, with only some meals, or not at all); and whether enzymes were effective at relieving GI symptoms. Subjects were asked to indicate the presence or absence of the following symptoms: diarrhea, steatorrhea (“fatty stools”), undesired weight loss, and delayed gastric emptying (as diagnosed by a physician), and whether or not GI symptoms interfered with their daily life.

A glycemic index was constructed based on the subject’s self-report of glycemic variability. One point was assigned for each of the following: self-reported hypoglycemic episodes necessitating assistance from another person to treat, episodes of seizure or loss of consciousness, and blood sugar readings >200 mg/dL. A score of zero was interpreted as minimal glycemic variability, and score of three as high glycemic variability.

Statistics

Summary data are reported as mean $\pm$ standard deviation. A mixed models approach was used to compare the proportion of subjects reporting symptoms at each follow up time point versus baseline prevalence. The mixed model approach accommodates missing data in longitudinal studies and takes into account the dependence of repeated within-subject measures. Logistic regression was used to analyze the relationship between enzyme dose and adherence on the presence or absence of GI symptoms, and the association of glycemic variability with GI symptoms. P-values ≤ 0.05 were considered significant. All analyses were performed using SAS[®] version 9.2 (Cary, NC, USA).

Results

Demographics

Subjects had a mean age of 34.4 ± 13.9 years (range 5–66 years) at the time of surgery. Seventy-four percent (n=136) were female. All subjects underwent TPIAT for a diagnosis of chronic or relapsing acute pancreatitis. The most common causes of pancreatitis were idiopathic chronic pancreatitis (36%), familial or genetic pancreatitis (18%), sphincter of Oddi dysfunction (17%), pancreas divisum (15%), cystic fibrosis (5%), and alcoholism (4%). TPIAT was performed at a mean of 7.4 ± 7.3 years after onset of pancreatitis. Prior lateral pancreaticojejunostomy had been performed in 23 (13%), distal pancreatectomy in 6 (3%), and Whipple procedure in 14 (8%). Most subjects had a history of prior ERCP (90%) and cholecystectomy (75%). Eighty-eight percent were on daily opioid analgesics at the time of surgery.

Pancreatic Enzyme Replacement Therapy

Sixty-two percent of subjects were prescribed and using pancreatic enzyme replacement therapy (PERT) before TPIAT. Prior to surgery, these subjects may have been taking enzymes either for pancreatic enzyme insufficiency, or for pancreatic suppression (pain control); our data does not allow us to determine the goal of pre-operative enzyme therapy. After TPIAT, 79% of subjects at any post-operative time-point reported *consistent* use of enzymes with all meals. Average reported enzyme doses over time are illustrated in Figures 1 and 2. Of note, while the most common enzyme intake after surgery was >1000 lipase units/kg/meal, by 2 and 3 years after surgery more than a third of subjects reported using <1000 lipase units/kg/meal.

GI Symptom Prevalence, Severity, and Enzyme Adherence

Prevalence of GI symptoms by time period is summarized in Table 1. Complaints were frequent before and after TPIAT. The most common symptom reported at any time point was diarrhea. At 12 months following surgery 80% of patients complained of diarrhea, 62% of steatorrhea, 41% of constipation, and 31% of weight loss or difficulty maintaining weight. Half of those affected felt that their GI symptoms interfered with daily life. After surgery, subject complaints of steatorrhea increased significantly, while complaints of constipation decreased (Figure 3). There was a statistically significant increase in frequency of complaint of steatorrhea from the pretransplant period at 3 months, 6 months, and 36

months post-TPIAT. Before surgery, 46% of subjects reported that one or more of these symptoms were severe enough to interfere with daily life, with 44–69% reporting GI symptoms severe enough to interfere with daily life at 3 months to 36 months after surgery.

The use of enzymes was marginally associated with a decreased likelihood of steatorrhea (odds ratio = 0.35; 95% CI 0.12 – 1.06; p value = 0.055). There was otherwise no significant association between enzyme adherence and report of GI symptoms (table 2). GI symptoms interfering with daily life did not differ based on subject self-report of adherence versus non-adherence to pancreatic enzyme replacement therapy (p=0.7). There was a strong association between enzyme dose and symptoms of constipation and weight loss. Enzyme dose and constipation were inversely related (higher doses of enzymes were associated with a lower prevalence of constipation post-TPIAT; p value = 0.055), while higher enzyme dose was directly associated with increase in self-reported weight loss (p value = 0.074). These findings may reflect a prescriber's bias to reduce enzyme dose in subjects struggling with constipation or to increase dose in those subjects struggling to gain weight.

There was no relationship between the occurrence of diarrhea and the prescribed enzyme dose. Over 60% of patients in our survey group reported the symptom of diarrhea. This symptom appeared to be independent of pancreatic enzyme dose, with similar incidence of diarrhea at both ends of the dosage range. Furthermore, as demonstrated in Figure 4, there was no decrease in percentage of subjects reporting diarrhea for those on higher doses of enzymes compared to lower doses. Weight loss was more common in subjects taking higher doses of enzymes, potentially reflecting a bias of physicians to prescribe higher doses of pancreatic enzyme therapy in subjects who were struggling to maintain their weight.

Pancreatic enzyme replacement therapy and GI symptoms in children

Pediatric demographics—The mean enzyme dose in children was similar to that seen in the entire population (data not shown); adherence to PERT for all meals and snacks was 92% at 3 months, 100% at 6 months, 69% at 12 months, and 80% at 2 years. Before surgery, diarrhea was present in 47%, steatorrhea in 28%, constipation in 56%, and weight loss or trouble gaining weight in 28%, with GI symptoms severe enough to interfere with daily life in 28% (Table 3). After surgery, diarrhea was more prevalent compared to pre-TPIAT baseline at 6 months (p=0.04), and steatorrhea at 6 months (p=0.005) and 1 year (p=0.008), but no differences were seen at all other time points. There was a trend towards fewer subjects reporting constipation by 2 years (20%, p=0.06), likely a consequence of discontinuing narcotic therapy.

Glycemic Variability—The association between glycemic variability and GI symptoms was assessed using a novel index for glycemic variability calculated from the diabetes section of the health questionnaire; one point each was assigned for the following: (1) any severe hypoglycemic episodes (requiring assistance from another person) in the prior 1 year, (2) any episode of seizure or unconsciousness in the prior 1 year, and (3) self-reported episodes of glucose > 200 mg/dL in the 4 weeks prior. A glycemic variability index of 0 in this cohort suggested euglycemia, in the absence of significant hyper- or hypoglycemia. Increased glycemic variability was associated with an increase in fatty stool symptoms as

depicted in Table 4. Those subjects with a glycemic variability index of 2 (15% of patients) had a 2.8 fold increased odds of steatorrhea (95% confidence interval 1.1– 7.0) compared to those with a glycemic variability index of 0, suggesting an important relationship between malabsorption and glycemic excursions.

Discussion

Chronic pancreatitis is a devastating disease with impact on physical functioning, psychological status, financial security, and social well-being [2,13–15]. Because the primary operative indications for TPIAT are relief of pain and restoration of a meaningful quality of life [3, 16–19], adequate management of postoperative GI symptoms remains paramount to the intervention's overall success. Our study reveals that the impact of postoperative exocrine complications is, perhaps, more pervasive than appreciated. Diarrhea, steatorrhea, weight loss, and constipation were commonly reported up to 3 years after surgery, despite adherence with pancreatic enzyme replacement therapy. These symptoms were severe enough to interfere with daily life in some, and malabsorption symptoms, in particular, contribute to glycemic lability.

These findings illustrate several key considerations for patients undergoing total pancreatectomy: 1) GI symptoms are common in patients with severe chronic pancreatitis, both before and after surgery and may be multifactorial; 2) proper PERT dosing and compliance are paramount in postoperative care; 3) failure to respond to PERT should trigger a search for secondary causes of malabsorption; and 4) GI symptoms in this population may have broad consequences affecting patients' daily functioning, macro and micronutrient absorption, and diabetes control which is of particular concern in this population at high risk of insulin-dependent diabetes.

All patients who undergo pancreatectomy must be on some form of pancreatic enzyme replacement [20]. Standard formulations include lipase, amylase, peptidase, and other enzymes in enteric-coated microspheres to facilitate appropriately timed intestinal transit and to prevent premature acid-mediated inactivation [4,7,9]. These medications are extremely costly, and must be taken with every meal and snack, both of which make patient adherence difficult [5]. Dosing range is 500–2000 lipase units/kg/meal or 2000–4000 lipase units/gram of fat in meal. Monitoring the efficacy of enzyme replacement therapy or the need for dosage-adjustment is difficult. The most reliable test is the 72-hour fecal fat assay, but patients find it very unpleasant and it is not suitable for repetitive testing. Optimal enzyme dose is clinically assessed by adequacy of weight gain and growth in children, and ability to maintain/regain a healthy weight in adults. Additional parameters, such as measurement of fat soluble vitamin levels, can identify subclinical malabsorption.

In our population, the average enzyme dose was within the usual prescribed and expected dosing range, but we observed great variability in PERT dose among individual patients within the cohort. Between 6 months and 3 years after TPIAT, as many as 40–45% of patients at any time point reported using <1000 lipase/units/kg meal, with around 10% taking <500 lipase units/kg/meal. These doses are likely inadequate for nutrient absorption following complete pancreatic resection. It appears that more TPIAT recipients were taking

<1000 lipase units/kg/meal than has been reported in cystic fibrosis, the most widely studied cohort of patients with exocrine insufficiency [10–11]. Adherence is critical—about 20% of patients in our population reported not using enzymes at all or not using enzymes with every meal. Our data is similar to that of Sikkens, et al., who found that, after pancreatic surgery, patients frequently received inadequate pancreatic enzyme replacement therapy (20).

Notably, diarrhea and weight loss were not helpful in determining adequacy of pancreatic enzyme use among TPIAT recipients. Some prescribers use the symptom of diarrhea as an indication to increase a patient's pancreatic enzyme dose, based on the belief that diarrhea is a marker for malabsorption, and that increasing the enzyme dose will decrease these symptoms. However, our data do not support the efficacy or validity of this practice. As illustrated in Figure 4 and Table 2, there was no relationship between the occurrence of diarrhea and the prescribed enzyme dose. This is similar to reports on the management of exocrine insufficiency in cystic fibrosis, where clinical abdominal symptoms and growth in children show little correlation to pancreatic enzyme dose [11]. Our data highlight the need for a protocol for PERT management, shared with the patient's primary care provider, to insure that patients achieve an appropriate enzyme dose after TPIAT, as well as good follow-up to optimize adherence.

Other gastrointestinal complications of TPIAT may cause abdominal pain and malabsorption. Pancreatectomy may impact complicated intrinsic neurohormonal regulation and result in asynchrony between gastric emptying and biliopancreatic secretion [4,5,20]. Post-operative narcotic use can also exacerbate dysmotility. The absence of pancreatic bicarbonate secretion may delay release of enteric-coated pancreatic enzymes to distal segments of the bowel, leaving little remaining transit area for nutrient absorption [4,6]. These factors are further complicated by wide variability among individuals with varying degrees of pancreatic resection and bowel reconstructions or bypasses [4,5,20,21]. All TPIAT recipients, in addition to pancreatectomy, undergo at least a partial duodenectomy most often with Roux-en-Y reconstruction, and some patients have preexisting comorbidities including inflammatory bowel disease or history of gastric bypass (data not presented) which may further complicate absorption. The above situations contribute to imperfections in mimicking normal pancreas function with PERT and may explain some of the persistent symptoms such as diarrhea or steatorrhea that occur at least occasionally in compliant patients on adequate lipase doses.

Potential solutions targeting persistent exocrine insufficiency are aimed at the aforementioned treatment barriers. Attention to dosing, education about enzymes, and regular follow-up may improve adherence. Enzymes are most effective when taken during and after a meal [9,22,23]. Several studies demonstrated improved lipid digestion with co-administration of acid-suppressing agents with non-enteric-coated enzymes [9,24–27]. Acid suppression in addition to enteric-coated formulations shows improved outcome over enteric-coated capsules alone and decreases required lipase dose [9,27]. Most studies have been done in patients with CF, who also have decreased intestinal and biliary bicarbonate secretion. In our practice, patients with adequate enzyme dose and continued pain and/or malabsorption are placed on a trial of a proton pump inhibitor after TPIAT.

If these strategies fail, diagnostic evaluation for other etiologies is warranted, including small intestinal bacterial overgrowth, giardiasis, blind loop syndrome, celiac disease, and other absorptive pathologies [4,9,20]. Digestive asynchrony provides a favorable environment for bacterial overgrowth [28,29]. Patients may present with diarrhea, gas, bloating, or steatorrhea. Our current protocol is to empirically treat for small intestinal bacterial overgrowth in patients who complain of these symptoms despite adequate titration of enzyme dosing.

This exploratory analysis identifies targets for clinical management protocols and future research. However, the data should be interpreted in the context of several limitations. The study relies on self-reported data; in particular, self-report may under- or overestimate the adherence with enzyme therapy. Stool testing, motility studies, and/or other diagnostic testing were not included in the analysis of this study. A number of the patients participating in this study underwent pancreatectomy prior to recent refinements in our postoperative clinical management, which has included closer GI physician involvement in patients' care and more aggressive treatment for residual GI symptoms. However, our findings highlight the need for a multidisciplinary approach in caring for this complex patient population, and the critical importance of close GI monitoring after TPIAT. Future studies may focus on further defining the problems affecting this patient population and proposing possible interventions.

Despite the ability of TPIAT to improve pain control and quality of life [2,3,16–19], GI symptoms post-operatively can be burdensome for a subset of recipients. Malabsorption seems to be associated with glycemic variability in these recipients, and could convey long-term risks of nutritional and vitamin deficiencies, or in the case of hyperglycemic excursions - islet graft burnout. Symptoms may be present even in patients who are adherent to adequate doses of enzyme therapy, suggesting consideration of alternative etiologies for steatorrhea and diarrhea. Our study identifies a need for further research and development in the treatment of exocrine pancreatic insufficiency, and for development of evidence-based guidelines essential to the ongoing management of this growing patient population.

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Abbreviations

CP	chronic pancreatitis
PERT	pancreatic enzyme replacement therapy
TPIAT	total pancreatectomy with islet autotransplantation
GI	gastrointestinal

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Figure 1.
Patient reported pancreatic enzyme dose (mean + standard deviation) expressed as lipase units/kg/meal at the time of surgery and for 36 months or more after surgery.

Figure 2.

Percentage of our cohort of post-surgical patients who were using a specific range of pancreatic enzyme (legend, in lipase units/kg/meal) at various times after TPIAT.

Figure 3.
Percentage of subjects reporting steatorrhea or constipation at specific times after surgery.
Points marked with an asterisk (*) are significantly different from baseline, $p < 0.05$.

Proportion of respondents across time points such that some patients may be represented more than once. Pooled from survey responses at 6 months (n=46), 1 year (n=55), 2 years (n=47), and 3 years (n=42).

Figure 4.

Percentage of TPIAT patients reporting one of four specific symptoms plotted versus reported pancreatic enzyme doses in lipase units/kg/meal.

Table 1

GI symptoms reported by adult patients following TPIAT

	Diarrhea		Steatorrhea		Constipation		Weight loss		Interfere with life	
	% of pts	p *	% of pts	p *	% of pts	p *	% of pts	p *	% of pts	p *
Pre-operative	69%	0.06	49%	0.03	66%	0.07	47%	0.80	46%	0.64
3 months	82%	0.09	66%	0.003	53%	<0.001	46%	0.98	44%	0.66
6 months	78%	0.17	75%	0.11	38%	0.001	46%	0.09	44%	0.69
1 year	80%	0.69	62%	0.14	41%	0.03	31%	0.30	51%	0.40
2 years	73%	0.11	67%	0.04	47%	0.01	37%	0.38	48%	0.16

* p-value for timepoint vs baseline

Table 2

Pancreatic enzyme intake and GI symptoms in TPIAT patients

Enzyme Intake IU Lipase/kg/meal	Diarrhea		Fatty Stool		Constipation		Weight Loss	
	n	(%)	n	(%)	n	(%)	n	(%)
< 500	28	(87.5)	25	(78.1)	14	(45.2)	12	(37.5)
500–999	38	(77.6)	32	(65.3)	22	(45.8)	14	(28.0)
1000–1499	32	(80.0)	27	(65.9)	20	(50.0)	17	(38.6)
1500–1999	12	(63.2)	11	(55.0)	5	(25.0)	8	(40.0)
2000	30	(83.3)	26	(72.2)	12	(33.3)	20	(54.1)

Proportion of respondents across time points such that some patients may be represented more than once. Pooled from survey responses at 6 months (n=46), 1 year (n=55), 2 years (n=47), and 3 years (n=42). Data is represented graphically in Figure 3.

Table 3

GI symptoms reported by pediatric patients and their parents

	Diarrhea		Steatorrhea		Constipation		Weight loss		Interfere with life	
	% of pts	p*	% of pts	p*	% of pts	p*	% of pts	p*	% of pts	p*
Pre-operative	47%		28%		56%		28%		28%	
3 months	61%	0.52	54%	0.07	46%	0.57	46%	0.28	23%	0.79
6 months	87%	0.04	87%	0.005	50%	0.87	38%	0.63	50%	0.27
1 year	83%	0.08	75%	0.008	50%	0.73	17%	0.52	50%	0.21
2 years	60%	0.51	50%	0.37	20%	0.06	40%	0.50	0%	0.07

* p-value for timepoint vs baseline

Table 4

Relationship between glycemic variability and presence of Steatorrhea.

Glycemic Variability Index	Odds Ratio	95% LCL	95% UCL
0	1		
1	1.92	1.04	3.54
2	2.78	1.11	6.96
3	3.97	0.81	19.5