

# Patient Demographics, Perioperative Testing, and Symptom Management in Total Pancreatectomy with Islet Autotransplantation: A Brief Review

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## Abstract

### Background

Chronic pancreatitis and its resultant pain, glandular dysfunction, and detriment to quality of life is a challenging and resource-intensive problem for health care systems despite the plethora of modalities developed to treat it. Removal of the gland and source of pain via total pancreatectomy is an effective, albeit drastic solution, with the potential for morbidity due to the complete loss of endocrine and exocrine function. The consequent "brittle diabetes" due to loss of endocrine function and glucagon-dependent counter-regulation may be ameliorated by autologous islet transplantation. Unfortunately, factors leading to optimal outcomes are poorly defined.

### Results

Data is mixed and limited to case series from institutions currently performing the procedure, but factors predictive of islet cell yields and overall insulin-independence include: disease etiology, metabolic status, and duration and severity of the disease. Imaging studies may prove an appropriate method for determination of pancreatic volume and disease complications prior to operative intervention. Although potentially overlooked, the resultant malabsorptive diarrhea, traditionally treated with pancreatic enzyme replacement therapy, is a significant barrier to postoperative quality of life and still requires further research and investigation.

### Discussion

Total pancreatectomy with autologous islet transplantation is a proven and effective method for treating those with intractable pain from chronic pancreatitis, but remains barred from widespread use due to cost, limited availability, and potential morbidity. Though great advances have been made, additional efforts at perioperative optimization, appropriate candidate selection and time to intervention must still be sought to further improve post-operative outcomes.

**Keywords:** Pancreatitis; Chronic; Pain management; Pancreatectomy; Transplantation; Autologous

**Abbreviations:**BSA: Body Surface Area; CP: Chronic Pancreatitis; CT: Computed Tomography; FSIWGTT: Fasting Sample Intravenous Glucose Tolerance Testing; HbA1c: Glycosylated Hemoglobin A1c; IAT: Islet Autotransplantation; IEQ: Islet Equivalent; IEQ/kg: Islet Equivalent per kilogram Recipient Body Weight; MMTT: Mixed Meal Tolerance Test; SMRCP: Secretin-enhanced Magnetic Resonance Cholangiopancreatography; MRI: Magnetic Resonance Imaging; PERT: Pancreatic Enzyme Replacement Therapy; ROC: Receiver Operating Characteristic; TP: Total Pancreatectomy; TPIAT: Total Pancreatectomy with Islet Autotransplantation; QoL: Quality of Life

## Introduction

Chronic pancreatitis (CP) is a debilitating condition characterized by progressive pancreatic inflammation, impairment of endocrine and exocrine function, abdominal pain, reduced Quality of Life (QoL), and increased health resource utilization [1,2]. Although patients can be managed with lifestyle changes, medical and endoscopic intervention, and neural blockade, surgical therapy is occasionally indicated for severe disease [3]. For patients without a single anatomical cause or disease refractory to prior operative interventions, total pancreatectomy (TP) provides definitive treatment and substantial long-term pain relief [4]. First employed in 1977 at the University of Minnesota, islet autotransplantation (IAT) has been employed to preserve  $\beta$ -cell function and combat the "brittle diabetes" resulting from the loss of both endocrine function and glucagon-dependent counter-regulation [5]. Although there is substantial potential benefit and demonstrated

improved long-term outcomes, outcomes, such as insulin and narcotic independence are variable (Table 1) and perioperative and patient-related factors associated with ideal outcomes are poorly defined.

## Factors predicting outcomes

Information regarding the outcomes of patients undergoing total pancreatectomy with islet autotransplantation (TPIAT) is limited primarily to retrospective case series which have demonstrated correlations between islet yield (in islet equivalents [IEQ]) and islet equivalents per kilogram of recipient body weight [IEQ/kg], lower body surface area (BSA [m<sup>2</sup>]), and female gender [4,6-8]. Large series have reported significantly higher islet yields in pediatric patients, possibly related to a decreased number of prior surgical interventions which are independently associated with higher rates of islet graft failure 1 year post-operatively [6].

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Group	Cincinnati [14]	Cleveland [12]	Baylor [11]	Minnesota [6]	Leicester [2]
Follow up time	5-years	Median of 27 mo. (3-66 mo.)	Mean of 23.7 ±2.2 mo.	36 months	Median of 11.5 years
Insulin Independence	27% (n=15)	33% (n=12)	41% (n=51)	Approximately 20%	19% (n=11)
Narcotic Independence	73% (n=41)	53% (n=19)	Not reported	70% 1-year postoperatively	45% (n=27)

**Table 1:** Outcomes after total pancreatectomy with islet autotransplantation (TPIAT).

Studied By							
Cleveland [12]		Baylor [11]			Minnesota [6]		
Patient Characteristics							
Insulin Independence		Comparing IEQ/kg <2,500 vs. >5,000			Islet graft failure (multivariate adjusted analysis)		
Variable	P-value	Variable	Spearman p	P-value	Variable	OR (CI)	P-value
Female gender	0.012	Duration of CP	-0.025	0.03	Alcoholic CP	3.25 (1.09-9.72)	0.035
Advanced disease on imaging	0.011	Comparing IEQ/kg <2,500 and either 2,500-5,000 or >5,000			IEQ/kg <2,000	28.4 (6.24-129)	<0.001
Mean IEQ	<0.001	Variable	Spearman p	P-value	Narcotic Use Post-Transplant (multivariate adjusted analysis)		
Mean IEQ/kg	<0.001	HbA1c	NR	<0.001	Variable	OR (CI)	P-value
					Prior Puestow	0.19 (0.05-0.66)	0.009
					≥3 prior stents	2.73 (1.10-6.79)	0.031

**Abbreviations:** CI=confidence interval; CP=chronic pancreatitis; DP=distal pancreatectomy; HbA1c=hemoglobin A1c; IEQ=islet equivalent; IEQ/kg=islet equivalent per kilogram patient body weight; NR=not reported; OR=odds ratio

**Table 2:** Factors predicting outcomes after total pancreatectomy with islet autotransplantation (TPIAT).

The etiology of CP is variably predictive, and patients with alcoholism or hereditary pancreatitis may have lower pancreas volumes, increased pancreatic structural changes, lower islet yields, and increased risk of islet graft failure, while those with idiopathic pancreatitis may have lower risks of islet graft failure [6,9,10]. Multiple studies have also demonstrated the relationship between longer disease duration and duration of narcotic use with low islet yield and graft failure (Table 2) [6,11]. Perhaps more subjectively, patients who reported more severely impaired physical health prior to surgery also had independently associated increased risk of islet graft failure and higher risk of impaired health at 1-year after TPIAT [6].

### Metabolic testing

Metabolic testing prior to surgery is often performed to establish a preoperative baseline for islet function and data suggest fasting glucose levels <100 mg/dL, C-peptide ≥4 ng/mL are associated with higher islet yields, and hemoglobin A1c (HbA1c) and mixed meal tolerance tests (MMTTs) are inversely correlated with IEQ/kg [10-12]. Moreover, fasting sample intravenous glucose tolerance testing (FSIVGTT) and MMTTs have been reported as significant predictors of islet mass ≥2500 IEQ/kg [10]. However, data is inconclusive and other studies have failed to identify significant correlations between total islet yield and perioperative with HbA1c, C-peptide, or glucose levels [13,14].

### Pre-operative imaging

Pancreas weight and gross fibrosis are correlated with lower islet yield and both factors negatively impact islet mass, however, these features are usually only determined intra-operatively [10,15]. Pre-operative imaging may be used to better predict islet function, IEQ yield, and post-operative outcomes. MRI and computerized tomography

(CT) scanning can generate 3-dimensional images of the pancreas and accurately calculate the volume of the pancreas, as well as assess for the presence of structural changes including: parenchymal calcifications, atrophy, and dilation of the main pancreatic duct. Islet yield has been understandably correlated with increased pancreatic mass, and mean islet yield has been reported to be decreased by 50% if any structural changes are demonstrated on imaging [9]. Calcifications in particular increase the odds of insulin dependence greatly, with only 15% of those with calcifications being insulin independent 1-year postoperatively [9]. Additionally, utilizing magnetic resonance imaging (MRI) and secretin-enhanced magnetic resonance cholangiopancreatography (SMRCP), features such as T1 signal-intensity ratio between the pancreas and paraspinal muscles and duodenal filling after secretin injection can accurately predict pancreatic fibrosis, islet mass, and subsequent islet yield [10,16].

### Pancreatic enzyme replacement therapy (PERT)

Although pancreatic enzyme replacement therapy (PERT) is routinely employed to counteract the loss of exocrine pancreatic function, patients continue to experience symptoms related to gastrointestinal malabsorption, including steatorrhea, weight loss, and glycemic variability. One study of 184 patients revealed that 80% of individuals reported diarrhea 1-year postoperatively and half felt that it interfered with their daily life [17]. In the same study, 72% of patients felt that their steatorrhea had increased significantly by 3-years postoperatively, however, the use of pancreatic enzymes was only marginally associated with decreased likelihood of steatorrhea (OR 0.35, 95% CI 0.12- 1.06, p = 0.055) [17]. Additionally, there was no significant association between increased GI symptoms and decreased (self-reported) adherence to pancreatic enzyme replacement therapy (PERT) (p = 0.7) [17].

## Discussion and Conclusions

There are still many barriers that limit the utility and outcomes of TPIAT and only a few highly experienced centers available are available to perform the operation. Insurance companies are often reluctant to cover the costs of islet isolation and many physicians are unfamiliar with the procedure or post-operative anatomy, physiology, or imaging, thus requiring patients to return to the TPIAT center for care and potentially resulting in delayed or absent follow-up [18,19].

Predictive factors suggest that when deciding on timing for TPIAT, delaying surgery is likely disadvantageous, as the duration of CP and worsening metabolic status are predictive of higher rates of graft failures and as more severely impaired patients are not likely to reach a normal state postoperatively. Factors suggestive of good outcomes should not necessarily limit patient selection but rather, should permit multidisciplinary health teams to assess candidacy and thereby provide appropriate pre-operative counseling and improved post-operative care, while still acknowledging and preparing for those at risk for poor outcomes.

Ultimately, TPIAT has proven benefit, with preservation of  $\beta$ -cell function and pancreas removal often resulting in insulin independence drastically improved QoL. However, there are still many questions to be addressed, including appropriate timing for TPIAT intervention, best practice for islet isolation and transplantation, and how to manage post-operative pain and gastrointestinal complications. With continued research into each facet of pre- and postoperative care, in addition to improved insight into optimal patient selection, TPIAT is a procedure adequately poised to address the CP as a societal healthcare burden and improve quality of life for patients.

## Disclosures

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