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Islet autotransplantation to preserve beta cell mass in selected patients with chronic pancreatitis and diabetes mellitus undergoing total pancreatectomy

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Abstract

Objectives—Islet autotransplant (IAT) is performed in non-diabetic patients with chronic pancreatitis at the time of total pancreatectomy (TP) to minimize risk of post-operative diabetes. The role of TPIAT in patients with chronic pancreatitis and C-peptide positive diabetes is not established. We postulate that IAT can preserve beta cell mass and thereby benefit patients with pre-existing diabetes undergoing TP.

Methods—Preoperative metabolic testing, islet isolation outcomes, and subsequent islet graft function were reviewed for 27 patients with diabetes mellitus and chronic pancreatitis undergoing TPIAT. The relationship between the results of preoperative metabolic testing and islet isolation outcomes were explored using regression analysis.

Results—Mean islet yield was $2,060 \pm 2,408$ IEQ/kg. Peak C-peptide (from mixed meal tolerance testing) was the strongest predictor of islet yield, with higher stimulated C-peptide levels associated with greater islet mass. Half of the patients who had C-peptide levels measured post-transplant demonstrated C-peptide production at a level that conveys protective benefit in type 1 diabetes (0.6 ng/mL).

Conclusions—These findings provide proof-of-concept that significant islet mass can be isolated in patients with chronic pancreatitis and C-peptide positive diabetes mellitus undergoing TPIAT. Stimulated C-peptide may be a useful marker of islet mass pre-transplant in these patients.

Keywords

islet; pancreatitis; transplant; diabetes; beta cell

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Introduction

For patients with severe chronic pancreatitis, total pancreatectomy (TP) and islet autotransplant (IAT) may be considered to relieve pain while preserving residual beta cell function.¹ In part because of the risk for brittle diabetes, total pancreatectomy is utilized only with severe pancreatitis refractory to medical or endoscopic interventions. A simultaneous islet autotransplant is performed to prevent or minimize the otherwise inevitable post-surgical diabetes; in this procedure, the islets are exocrine pancreas is mechanically and enzymatically disrupted and the isolated islet are infused into the portal vein of the liver where they engraft and function over weeks to months. In non-diabetic recipients, one-third achieve insulin independence but the majority demonstrate at least partial graft function (either C-peptide positive or low dose insulin therapy).² This procedure has traditionally been reserved for patients who are non-diabetic prior to surgery.

However, chronic pancreatitis can result in a slow progression to endocrine insufficiency and diabetes mellitus.³ The lifetime risk of diabetes mellitus is variable but may exceed 70% depending on the etiology of disease.^{4, 5} This form of diabetes, called type 3c or pancreatogenic diabetes, results from a partial or complete insulinopenia due to progressive pancreatic compromise.⁶ Pathologically it differs from type 1 diabetes in which complete insulin deficiency results from autoimmune destruction of the beta cells and from type 2 diabetes in which insulin resistance is a major component. For patients with chronic pancreatitis and diabetes who have islet function (C-peptide positive), the role of an IAT at the time of pancreatectomy is unclear. Many centers will perform total pancreatectomy without islet transplant in these patients, thereby sacrificing residual islet function for pain relief. The result is complete insulin and glucagon deficiency, and possibly labile diabetes.⁷ No studies in the medical literature explore the role of IAT in these patients to preserve endogenous beta cell function.

Studies in patients with type 1 diabetes document a clear benefit to preserved islet function. Those with type 1 diabetes who retain a C-peptide at a minimal level (0.6 ng/mL stimulated) have, on average, lower hemoglobin A1c levels, lower rates of microvascular complications, less risk of diabetic ketoacidosis, and fewer episodes of severe hypoglycemia.^{8,9} Type 1 diabetes mellitus and surgical diabetes share the feature of insulin deficiency. Thus, one could postulate that retaining islet function after total pancreatectomy may have a similar benefit as to that seen in type 1 diabetics.

At our center, we have performed IATs at the time of total pancreatectomy in patients with pre-existing C-peptide-positive diabetes mellitus, with the goal to preserve beta cell mass and some degree of endogenous islet function. Herein, we report our experience with islet transplant in these recipients, and explore preoperative variables that may help predict those patients in which islets can be successfully isolated and transplanted.

Methods

Subjects

Medical history and laboratory data were reviewed for all diabetic patients undergoing TP-IAT for the management of chronic pancreatitis between October 1985 and May 2011. Patients were considered to have diabetes mellitus if one of the following criteria were met: 1) physician-assigned diagnosis of diabetes mellitus prior to surgical evaluation, 2) elevated fasting blood sugar >125 mg/dL at consultation or preoperative visit, confirmed by repeat testing, or 3) hemoglobin A1c (HbA_{1c}) level ≥ 6.5% at consultation or preoperative visit. In all, 27 patients met inclusion criteria for diabetes mellitus. Patients were enrolled in one of

two study protocols for follow up of outcomes after pancreatectomy and IAT at U of MN. Study protocols were approved by the University of Minnesota Institutional Review Board.

Total Pancreatectomy and Islet Isolation

Since 2007, all patients received preoperative evaluation and multidisciplinary review for appropriateness of TP-IAT using indications as previously published.¹⁰ The procedure of TP-IAT is described in greater detail elsewhere.^{1, 11} Islet isolation and purification was performed in the University of Minnesota Molecular and Cellular Therapeutics GMP facility. Briefly, the pancreas was distended with cold enzyme solution using a pressure-controlled pump system¹² and then digested using the semi-automated method of Ricordi.¹³ The number of islets were quantified as islet equivalents (IEQ), which is islet mass standardized to an islet size of 150 micrometer diameter. Islet yield was considered in the analysis as total IEQ and IEQ per kilogram recipient body weight (IEQ/kg).

Laboratory measures of glycemic control and islet function

Since October, 2006, all patients undergoing pancreatectomy and IAT had routine preoperative assessments including HbA_{1c} level and mixed meal tolerance test (Boost HP, 6 mL/kg to maximum of 360 mL) with glucose and C-peptide drawn fasting and at 1 and 2 hours after Boost HP. Patients continue on their usual basal insulin for this test, but short-acting or rapid-acting insulin is withheld until completion of testing. Prior to 2006, HbA_{1c}, fasting glucose, and fasting C-peptide were available for some participants. In all, HbA_{1c} was available for 21 patients, C-peptide and glucose values in 18 patients.

Since the time that C-peptide testing was initiated (2006), only patients with C-peptide positive diabetes mellitus were considered candidates for IAT. Prior to 2006, patients who did not require insulin or used low doses of insulin were assumed to have endogenous islet function (presumably C-peptide positive) and were considered candidates for the procedure.

Post-Transplant Islet Function

Follow up data was reviewed for insulin use, HbA_{1c} levels, and glucose and C-peptide levels (fasting and stimulated, mixed meal tolerance test). Only laboratory data obtained >2 months post-transplant were considered in the analysis, as earlier measures may be affected by intensive glucose control during hospitalization and incomplete islet engraftment early posttransplant. C-peptide, the primary indicator of post-transplant graft function, was available for 16 cases.

Statistical Analysis

Summary data is reported as mean $\pm$ standard deviation. The relationship between continuous preoperative variables and islet yield were analyzed by Pearson's correlation coefficients. Mean islet yield by categorical variable were compared with student t-tests. Chi-square tests were used to analyze the relationship between peak C-peptide pre-transplant (above or below median) and C-peptide positivity post-transplant. P-values $\leq$ 0.05 were considered significant. All analyses were performed using SAS® version 9.2.

Results

Patient Characteristics

Twenty-seven patients age 17- 72 years (mean age 44 ± 15) were included in the analysis. Twenty-four (89%) were female. Mean BMI was 26.8 ± 6.5 kg/m². Disease was most often idiopathic (n=11), with the other most common etiologies identified as sphincter of oddi dysfunction (n=4) and familial disease (n=3). Ten had one or more prior pancreatic

surgeries, including lateral pancreaticojejunostomy (n=6), distal pancreatectomy (n= 3), or Whipple procedure (n=2). Preoperative HbA_{1c} level was $6.9 \pm 1.5\%$ (table 1). Sixteen patients were treated with insulin therapy and 12 with oral anti-diabetic medications. Mean islet yield was $144,041 \pm 157,559$ IEQ and $2,060 \pm 2,408$ IEQ/kg. Islet yield was lower in those with pre-existing diabetes compared to non-diabetic IAT recipients (n=356, mean $3,780 \pm 3,517$ IEQ/kg, $p=0.0006$). Mean hospitalization postoperatively was 17 ± 11 days. There were no perioperative mortalities.

At most recent follow up (mean 24 ± 34 months, range 3 months- 11 years), 78% of patients described pain as resolved or better than prior to pancreatectomy, and 78% of those responding to a health questionnaire described their general health as improved or much improved.

Relationship between preoperative variables and islet mass isolated for IAT

Both fasting and stimulated C-peptide before surgery correlated significantly with islet yield (IEQ/kg), while fasting and stimulated glucose values and HbA_{1c} levels did not correlate with IEQ/kg (table 1). There was a trend towards a weak association of fasting glucose with IEQ/kg that was not statistically significant in this small data set. The most important predictor of islet yield was the peak stimulated C-peptide from a 2-hour mixed meal tolerance test. Islet yield was predicted from peak C-peptide using the following formula: $\text{IEQ/kg} = -937.6 + 573.5 * \text{Peak C-peptide}$ ($r = 0.76$, $p\text{-value} = 0.0004$; figure 1).

Mean islet yield was lower in patients who required insulin treatment before surgery, compared to non-insulin dependent diabetics ($1,020 \pm 2,776$ IEQ/kg vs $3,573 \pm 1,441$ IEQ/kg, $p=0.004$). However, in the recent era (2009-present), insulin therapy was routinely initiated before surgery in nearly all diabetic patients. Patient age and BMI were not important predictors of islet yield.

Islet graft function post-transplant

As expected, all patients remained diabetic after TP- IAT, and all patients required insulin therapy. However, the majority retained some islet graft function (table 2). Laboratory data for HbA_{1c} and C-peptide were available for 16 patients. At the most recent follow up (mean 9.7 ± 8.9 months), C-peptide levels were 0.3 ng/mL, a standard used for establishing islet function in allogeneic islet transplants¹⁴, in 13 of 16 (81%). Nine (56%) had C-peptide levels 0.6 ng/mL, the minimum value found to convey a favorable benefit on glycemic outcomes and complications in type 1 diabetics⁹. Those patients with a preoperative peak C-peptide at or above the median value (5.4 ng/mL) were more likely to have a post-transplant C-peptide value 0.6 ng/mL ($p=0.07$). Mean HbA_{1c} value was $7.4 \pm 1.6\%$, fasting glucose 134 ± 38 mg/dL, fasting C-peptide 0.4 ± 0.5 ng/mL, and peak C-peptide (fasting or stimulated) 1.2 ± 1.3 ng/mL (range, undetectable to 4.0 ng/mL).

Discussion

Islet autotransplant is performed to preserve endogenous beta cell function in patients with chronic pancreatitis undergoing total pancreatectomy. The therapeutic value of IAT is recognized for patients with chronic pancreatitis without endocrine insufficiency.^{1,15} The role of IAT in patients with C-peptide positive diabetes undergoing TP for CP has not been established. In this small series of patients, we provide proof of principle that islets can be successfully isolated even in those with diabetes and that islet function can be retained in at least half.

IAT introduces minimal risks to the patient beyond that incurred with pancreatectomy alone. Additional anesthesia time is required for IAT, and there is a small risk of portal thrombosis

particularly if heparinization is not employed.¹⁶ However, economic costs may drive careful selection of diabetic recipients for this procedure. Although our data is preliminary and insufficient to exclude anyone other than C-peptide negative diabetics from IAT, these data suggest that preoperative measurements may be useful in predicting successful islet isolation outcomes. Higher stimulated C-peptide was associated with higher islet yield and greater likelihood of islet function (as measured by C-peptide production) post-transplant. Glycemic control, as measured by the preoperative A1c and glucose were much less important than C-peptide levels, and thus should not be used to exclude potential recipients. However, one must use caution in interpreting C-peptide levels alone in any individual, as a low C-peptide in the context of *normal* glucose tolerance may be normal for an insulin sensitive individual.

Extrapolating from studies in type 1 diabetes mellitus, we postulate that preserving islet function in these patients with chronic pancreatitis undergoing total pancreatectomy may reduce the risk for brittle diabetes post-transplant and convey an overall benefit to glycemic control. In the 16 cases in this small series where post-operative C-peptide was measured, we observed 80% of recipients with some graft function (>0.3 ng/mL, based on the Collaborative Islet Transplant Registry which defines <0.3 ng/mL as complete graft failure)¹⁴, and over half had C-peptide levels of >0.6 ng/mL. This latter threshold is particularly critical as data from the Diabetes Control and Complications Trial and other studies in type 1 diabetics document an overall better outcome when C-peptide is present at >0.6 ng/mL. Patients with T1D and preserved C-peptide have lower HbA_{1c} levels, fewer microvascular complications, lower incidence of DKA, and a $>60\%$ reduction in severe hypoglycemia compared to T1D patients who are negative for C-peptide or have levels <0.6 ng/mL.^{8,9}

Currently we are limited to extrapolating from studies in type 1 diabetes. Metabolic follow up data in our IAT recipients remains of short duration, and long-term follow up will be needed to document prolonged benefit. Average HbA_{1c} in our recipients was above the ADA goal of 7%. Intensive insulin therapy and maintenance of goal or near goal HbA_{1c} may be critical to the preservation of islet function, to avoid the effects of glucotoxicity on the remaining beta cell mass.^{17,18} It is promising that some diabetic IAT recipients have clinically significant C-peptide production early after transplant, with C-peptide levels documented as high as 4 ng/mL post-transplant. However, it is important to counsel patients appropriately before the procedure, as they are potentially trading one form of diabetes (pancreaticogenous diabetes) for surgically-induced type 1 diabetes, which could be labile, particularly if the islet graft fails.

While the data is promising that IAT can preserve endogenous islet function for some time after TP even in those with pre-existing pancreaticogenous diabetes, this data should be interpreted within the context of the study limitations. This was a retrospective analysis with mostly short duration of follow up. The number of cases with sufficient data was too small to permit a multivariate analysis. Importantly, no randomized trial has established the benefit of IAT in those with pre-existing diabetes, and we do not know how long the islet grafts will continue to function.

In conclusion, we demonstrate in this preliminary analysis the ability to successfully isolate and transplant islets in a number of patients with diabetes mellitus and chronic pancreatitis undergoing total pancreatectomy. Those patients who are C-peptide positive should be considered as potential candidates for IAT before TP alone is performed. The level of C-peptide production before surgery may be a key variable in determining which patients are likely to have an adequate islet yield to justify the procedure. Further follow up will be necessary to determine selection criteria and better define long term benefit of IAT in diabetic CP patients.

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Figure 1.

Islet equivalents per kilogram body weight (IEQ/kg) isolated and transplanted in diabetic IAT recipients versus the pre-surgical peak C-peptide (stimulated value from mixed meal tolerance testing). The solid line indicates the predicted IEQ/kg based on preoperative C-peptide, predicted from the equation: **IEQ/kg = -937.6 + 573.5 * Peak C-peptide**. Pearson's correlation coefficient (r) = 0.76, p -value = 0.0004.

Table 1

Mean preoperative metabolic test results and islet yield for diabetic TPIAT recipients, and the association of glucose, C-peptide, and HbA_{1c} values before surgery with islet yield. Only C-peptide values correlated significantly with islet yield at the time of TPIAT.

Baseline Parameter:	<i>n</i>	Mean (SD)	Correlation with IEQ/kg (r)	p value
IEQ/kg	27	2,060 (2,408)	NA	NA
HbA _{1c} (%)	21	6.9 (1.5)	-0.21	0.35
Fasting C-peptide (ng/mL)	18	2.7 (2.0)	0.53	0.02
Peak C-peptide (ng/mL)	17	5.2 (2.0)	0.76	0.0004
Fasting glucose (mg/dL)	18	129 (41)	-0.32	0.19
Peak glucose (mg/dL)	16	194 (68)	-0.25	0.35

Table 2

Age (y)	Sex	Weight (kg)	BMI (kg/m ²)	Etiology	Prior Surgery	Treatment (pre-op)	Baseline Labs				Post-operative Labs						
							HbA1c (%)	Fasting CP (ng/mL)	Peak CP (ng/mL)	Fasting glucose (mg/dL)	HbA1c (%)	Fasting CP (ng/mL)	Peak CP (ng/mL)	Fasting glucose (mg/dL)			
60	F	44	16.2	Idiopathic	yes	Insulin											
47	F	54	21.9	Biliary	yes	Insulin	9.5										
32	F	45	17.4	idiopathic	no	Lifestyle	5.4		71								
36	F	70	26.7	Hyperlipidemia	no	Oral meds	5.2										
55	F	70	26.3	Biliary	yes	Insulin	6.8										
19	F	105	39.5	Familial	yes	Insulin and Oral meds		3.7									
29	F	67	26	Familial	no	Insulin											
41	F	88	31.3	Idiopathic	no	Oral meds											
44	F	49	17	idiopathic	no	Insulin								5.9		0.6	
43	M	69	20.1	Alcohol use	yes	Oral meds	5.6										
43	F	85	34.4	Idiopathic	yes	Oral meds	5.2	8.1	86	7.4	0.5	2.8					102
47	F	70	25.9	Idiopathic	no	Oral meds	6.2	6	137		0.7	4					100
17	F	77	31.1	idiopathic	no	Insulin	6.3	1	98	9	0.1	0.5					136
53	F	90	33	SOD dysfunction	no	Oral meds	6.6	4.4	92	7	0.4	0.4					140
57	F	77	27.1	Idiopathic	yes	Lifestyle	5.6	3.3	100	6.2	0.3	0.8					120
44	F	87	37.7	Hyperlipidemia	no	Lifestyle	8.7	3	224								
28	F	53	20.8	SOD dysfunction	no	Insulin and Oral meds	6.7	0.7	108	9	0.1	0.3					126
24	M	119	35.5	SPINK1 and CFTR mutations	yes	Insulin	5.5	0.5	101	6.8	<0.05						182
49	F	77	31.1	SOD dysfunction	no	Oral meds	6.6	1.9	114	7.4	0.1	0.4					89
17	M	73	22.8	Familial (PRSS1)	yes	None	5	2.2	127	11.4	0.7	0.7					106
45	F	100	34.1	SOD dysfunction	no	Insulin	7.5	1.4	117	8.2	0.4	0.8					216
59	F	61	21.1	Idiopathic	no	Insulin	8.8	3.4	144	5.5	1.8	3.8					96
53	F	74	29.6	Idiopathic	no	Insulin and Oral meds	8.1	2.2	206								
67	F	61	22.3	Idiopathic	no	Insulin and Oral meds	7.7	1.2	151	8.1	0.1	0.1					137
51	F	63	20.6	Alcohol use	yes	Insulin	6.4	1.4	163	7.3	0.1	0.15					179

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Case #	Age (y)	Sex	Weight (kg)	BMI (kg/m ²)	Etiology	Prior Surgery	Treatment (pre-op)	Baseline Labs				Post-operative Labs			
								HbA1c (%)	Fasting CP (ng/mL)	Peak CP (ng/mL)	Fasting glucose (mg/dL)	HbA1c (%)	Fasting CP (ng/mL)	Peak CP (ng/mL)	Fasting glucose (mg/dL)
6	72	F	64	25.9	Obstruction (duodenal adenoma)	no	Insulin	4.8 [*]	1	2.5	125	4.9 [*]	0.3	2.6	108
9	52	F	80	29.4	Alcohol use	no	Insulin and Oral meds	10.6	3.9	6.3	164	6.5	0.9	1.5	180

alents, IEQ/kg = islet equivalents per kilogram body weight, BMI= body mass index, HbA1c= glycosylated hemoglobin, CP= C-peptide.
ted to non-pancreatic disease, possibly contributing to spuriously low HbA1c.