PANCREAPEDIA
Exocrine Pancreas Knowledge Base

APA AMERICAN PANCREATIC ASSOCIATION

Total Pancreatectomy and Islet Auto Transplantation for Chronic Pancreatitis

Sydne Muratore, Martin Freeman, and Greg Beilman

Departments of Surgery and Medicine, University of Minnesota, Minneapolis, MN, USA

e-mail: beilm001@umn.edu, freem020@umn.edu

Version 1.0, February 20, 2015 [DOI: 10.3998/panc.2015.8]

1. Introduction

Surgical management of chronic pancreatitis is in a constant state of evolution. The trials of management are akin to the inherent complexity of the organ's function and closeness to neighboring organs. As the progressive and irreversible process of chronic pancreatitis commences, patients are subjected to varying degrees of endocrine and exocrine loss, as well as pain. Management of this process is multifaceted. Endoscopic and surgical drainage procedures can be used to attempt decompression of dilated ducts. Celiac ganglion blocks, narcotic analgesics, and enteral or parenteral nutrition are therapies directed at the recurring or continuous pain of recurrent acute pancreatitis (RAP) or chronic pancreatitis (CP). Patients refractory to these therapies frequently find themselves on escalating doses of narcotics due to intractable pain and can be faced with countless days of lost time at school or work, depression, and financial burden.

2. History

Total pancreatectomy was first proposed to relieve pain in patients where other therapies had failed (28). Islet autotransplantation was added to this procedure to preserve beta-cell mass in an effort to prevent development of brittle diabetes (28,120). Mirkovitch and Campiche were the first successful investigators to transplant autologous islets in large animals by injecting into the spleens of pancreatectomized dogs (115, 164). The first human total pancreatectomy with islet autotransplantation (TPIAT) in the world was performed at the University of Minnesota in 1977. This patient was insulin-independent and pain-free until her death 6 years later due to unrelated causes (56,121). This success helped to shed light on the etiology of antecedent allograft efforts; failure likely resulting from low viability, poor preservation of deceased donor pancreases, or rejection (28,121). A small number of other centers began utilizing IAT after TP with variable initial success in the 1980s, with modest program expansion occurring in the 1990s-2000s (164). Complications initially occurred at some centers not using anticoagulation (112,114,173). The world literature as of 2014 contains reports of over 900 IATs as several centers are developing their programs (9,10,52,68,71,82,86,99,116,162,163,168,183,198). Advancements in surgical technique, islet isolation, patient selection, and perioperative care are steadily improving outcomes for this therapy.

3. Patient Selection

Patient selection for TPIAT is difficult. The primary focus for surgery is to alleviate pain, however, the pathogenesis of pain in chronic pancreatitis is incompletely understood. There are multiple theories based on observational studies that attempt to explain the multifactorial features of this prominent symptom. In the presence of strictures,

stones, or disrupted ducts; increased intraductal pressure, interstitial hypertension, and ischemia are thought to be the culprits of pain. The neuropathic theory is based on observation of abnormal intrapancreatic nerves and increased perineural inflammatory cells (124, 88, 176). Additionally, pain levels do not correlate well with severity of fibrosis or impairment of organ function (18). These inconsistencies contribute to the complexity of patient selection for TPIAT. Individualized evaluation is critical for optimal pairing of appropriate therapy. Patients with dilated large ducts or expanded head may be candidates for endoscopic or surgical drainage procedures. Those with a focal stricture, disrupted duct, or tail-only disease may find relief when treated with distal pancreatectomy (128). However, there are a growing number of patients not candidates for classical surgical therapy or endoscopic drainage, including small duct pancreatitis and minimal change disease. Additionally, adults and children with genetic causes of chronic or recurrent pancreatitis should be given special consideration for TPIAT, given the likelihood of persistent disease, and in some patients increased risk for pancreatic malignancy (18).

4. Preoperative Evaluation Criteria

Given the gravity of removing the entire pancreas, the correct diagnosis of CP is paramount to the success of this operation. Criteria for patient selection has evolved over the years as outcomes and better understanding of the disease process help match patients to the appropriate surgical management. Patients should be evaluated at a well-established center with a multidisciplinary approach including surgeons, gastroenterologists, endocrinologists, pain management physicians, and nurse coordinators. Patients should have abdominal pain > six months duration with impaired quality of life such as inability to attend work, school, or ordinary activities; repeated hospitalizations; and a constant need for narcotics. Their symptoms must have failed to respond to medical or endoscopic therapies.

The University of Minnesota has developed the following criteria for the diagnosis of chronic pancreatitis **(Table 1)**: 1) Pancreas calcifications on CT scan , or obviously abnormal ERCP including pancreatic stones, strictures and/or main duct/sidebranch abnormalities, or greater than or equal to six of nine criteria on endoscopic ultrasound (EUS); 2) Two of three of the following: ductal or parenchymal abnormalities on secretin stimulated magnetic resonance cholangiopancreatography (MRCP), EUS with four of nine criteria positive, abnormal endoscopic pancreatic function tests with peak bicarbonate < 80 mmol/L).; 3) Histopathologic confirmed diagnosis of chronic pancreatitis from previous operations or biopsy; 4) Hereditary pancreatitis (PRSS1, SPINK1, or CFTR gene mutation) with a compatible clinical history; or 5) History of recurrent acute pancreatitis with greater than three episodes of pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase three times normal (19,162). EUS evaluation features include “Rosemount Criteria”: hyperechoic parenchymal foci, strands, hypoechoic lobules, cysts, main duct irregularity, ductal dilation, hyperechoic duct walls, visible side branches, and calcifications or stones (37).

Contraindications include active alcoholism, pancreatic cancer, illegal drug usage, poorly controlled psychiatric illness, predictable inability to comply with the postoperative regimen, or end stage cardiopulmonary disease (18,162). Patients with C-peptide negative diabetes also do not benefit from the IAT portion of the procedure, therefore it is not recommended at this time (28). Additionally, preoperative assessment for liver disease; including portal hypertension, portal vein thrombosis, or cirrhosis is important as these are relative contraindications to any major pancreatic resection or islet embolization into the portal vein (18).

Table 1: University of Minnesota Criteria[163]
To be considered for TPIAT, patients must meet criteria in sections I and II and have no contraindications:

I. Definitions (must have one of the following: a, b, or c)

a. CP (must have one of i, ii, or iii) Patients with chronic abdominal pain, lasting > 6 months, features consistent with that of pancreatitis, and evidence of CP as evidenced by at least one of the following:
   i. Morphologic/functional evidence of CP [CT of abdomen with evidence of CP (calcifications), or ERCP evidence of pancreatitis]
   or
   ii. EUS of ≥ 6/9 criteria positive of CP
   or
   iii. At least 2 of the following 3 findings:
      1. Secretin MRCP or ERCP, with findings suggestive of CP (abnormal duct/side branch) or MRI T2 evidence of fibrosis
      2. EUS with ≥ 4/9 criteria positive for pancreatitis
      3. Abnormal exocrine pancreatic function tests (peak bicarbonate < 80)
   or

b. Relapsing AP (must have both 1 and 2)
   i. Three or more episodes of documented AP with ongoing episodes over > 6 months.
   ii. No evidence of current gallstone disease or other correctable etiology such as autoimmune pancreatitis
   or

c. Documented hereditary pancreatitis with compatible clinical history.

II. Indications for TPIAT (must have each of the following: 1-5)

a. Documented CP or relapsing AP with chronic or severe abdominal pain, directly resulting in at least one of the following:
   i. Chronic narcotic dependence (patient requires narcotics on a daily or nearly daily basis for > 3 months)
   ii. Impaired quality of life, defined by at least one of the following:
      1. Loss of job
      2. Inability or significantly reduced ability to work or attend school
      3. Frequent absences from school
      4. Frequent hospitalizations
      5. Loss of ability to participate in usual age-appropriate activities
   iii. Complete evaluation, with no reversible cause of CP or relapsing AP present or untreated
   iv. Unresponsive to maximal medical therapy and endoscopic therapy, with ongoing abdominal pain requiring routine narcotics for CP or relapsing AP
   v. Adequate islet cell function (non-diabetic, or non-insulin-requiring diabetes with C-peptide positive)

5. Metabolic Testing

After determining that recurrent acute pancreatitis or chronic pancreatitis is the primary diagnosis and the pain is of pancreatic origin, evaluation of metabolic function should be undertaken prior to surgery. This may include fasting and postprandial blood glucose and HbA1c, glucose tolerance test, and baseline and stimulated C peptide levels. Studies have demonstrated that fasting and mixed meal test glucose and HbA1c correlated inversely with IEQ/kg, while the other factors have modest correlation with islet isolation outcomes as well (14,16,102).

6. Other Testing

Immunization status should be assessed and updated to include encapsulated organisms due to the high likelihood of splenectomy associated with removal of the pancreas. Additionally, assessing nutritional status and for comorbidities that may impact postoperative management, such as gastroparesis, is important. Exocrine dysfunction is common in preoperative CP patients, however, no routine quantitative preoperative testing is performed at this time. In patients with cystic fibrosis mutations, pulmonary consult for evaluation and preoperative optimization is appropriate.

7. Technique

TPIAT is most commonly performed via open laparotomy, though increasing reports of laparoscopic and robotic assisted resection are being described (69,106,74,66,65,203). Surgery involves resection of the entire pancreas, duodenum, distal common bile duct, and typically the spleen. Pylorus preservation is surgeon dependent. During mobilization of the pancreas, an important consideration is that the blood supply must be preserved as long as possible to minimize warm ischemia time to the islet cells. In this way, the gastroduodenal artery and the origin of the splenic artery and splenic vein are ligated only after full pancreatic mobilization. The distal pancreas should not be separated from the splenic vessels (28). In cases of difficult mobilization, the body and tail can be resected and sent separately to the islet processing lab while the head is removed and sent later (162,199). After resection, the specimen is placed in cold preservation solution and prepared for processing by removing non-pancreatic tissue before being sent to the lab (15). Biliary and enteric reconstruction occur while the islets are being processed. Choledochojejunostomy is typically performed in the end-to-side fashion. Gastrojejunostomy or duodenojejunostomy can be performed in the antecolic or retrocolic fashion. Variations of reconstruction have been described when the patient's anatomy or sequela of chronic pancreatitis necessitate alternative resections (163).

Spleen resection rates are variable across centers, but is necessary the majority of the time due to disruption of the blood supply (162,183). After the hilar vessels are taken, the spleen can at times survive off collateral circulation. Leaving the spleen has its risks, however, including variceal formation, splenomegaly, and both early and late GI bleeding (28,68).

After processing the pancreas for islet isolation, the islets are returned to the operating room for infusion. The majority of centers perform this infusion through the portal vein with embolization of islets to the liver. There are multiple options for endovascular access site to the portal vein, such as a recanalized umbilical vein (136), mesenteric vein (3,168,184), or splenic vein (117). Islets are typically infused intraoperatively, or less commonly by interventional radiology after surgery. This is done via percutaneous transhepatic access to the portal vein (117,163). Heparin is administered at 70 U/kg prior to infusion to minimize thrombotic complications from tissue thromboplastin present in the islet preparation (28,112). Most centers also measure portal pressures before and during infusion. If there is a persistent increase in portal pressure > 25cm H20 with islet infusion, it is advisable to consider an alternative site such as intraperitoneal, beneath the renal capsule, or the sub-mucosal layer of the stomach (28).

8. Preoperative Care

Continuous insulin infusion is initiated immediately after resection of the pancreas to maintain euglycemia and prevent glucose toxicity to the islets as they engraft (14,199). This is continued postoperatively until the patient has initiated enteral nutrition and may be transitioned to an outpatient regimen. A gastric or jejunal feeding tube may be placed at the discretion of the surgeon at the time of operation. Exocrine supplementation

may be administered upon initiation of enteral feeding as well from either route. At the discretion of the surgeon, prophylactic heparin/lovenox should be initiated in the postoperative period when bleeding risk allows. It is the practice of the author's institution to perform a screening right upper quadrant ultrasound at one week postoperatively to evaluate for portal vein thrombosis. If positive, patients are kept on Coumadin for three months.

9. Islet Isolation

Islet isolation and purification must be performed at a facility that meets good medical practice (GMP) standards and has expertise in islet isolation. The basic method of islet preparation will be reviewed, however, enzyme type varies across institutions. First, intraductal infusion of enzyme is performed either manually or via automated pump perfusion. Interstitial perfusion is performed in cases of severe fibrosis or incomplete enzyme dispersion. Next, semi-automated digestion at 34-37°C in a Ricordi chamber facilitates tissue dissociation. Previously, Liberase HI was universally adopted for enzyme digestion from 1994 to 2007. At this point, it became clinically unavailable and centers now utilize a range of enzyme protocols (5,8).

After digestion, purification is performed to minimize exocrine cell contamination without compromising islet numbers. Islet purification is performed using isopycnic density gradient centrifugation (5,8). The islets can also be partially purified or transplanted as an unpurified preparation. The decision to purify is multifactorial, balancing the benefit of avoiding islet exposure to harsh solutions and additional mechanical stress and the desire to minimize increases in portal pressure during islet embolization to the liver. Currently, the author's institution allows up to 0.25 ml/kg for intraportal infusion. Quantities above this are considered for purification (8,197).

Extent of fibrosis plays a large role in enzymatic digestion of the extracted pancreas. Additionally, age, pancreas weight, and fat infiltration can lead to discrepancies in islet release. Variations in length of enzyme exposure, enzyme dose, digestion chamber size, temperature, circulation speed, and level of mechanical shaking are needed in order to accommodate the discrepancies found in each organ (8).

10. Outcomes

The majority of TPIATs reported to date have been performed at the University of Minnesota, encompassing over 500 patients (163). Other reports of current or past TPIAT programs include centers at Leicester, University of Cincinnati, University of Arizona, University of Alabama, Medical University of South Carolina, Digestive Disease Institute Cleveland, and Baylor Research Institute (68,198,71,52,116,183,168). TPIAT for small numbers of patients with benign and malignant tumors are being performed at San Raffaele Scientific Institute in Italy (9,10) and benign tumors in Korea (82,86,99) and Geneva (24).

Examining the demographics **(Table 2)** in the largest series with comprehensive data of TPIAT for CP, patients with mean ages 35 - 44 undergo surgery after suffering symptoms of pancreatitis for a range of 5.4 to 9.2 years (162,68,168). The most common etiology prior to surgery is idiopathic, followed by alcoholic pancreatitis. Anywhere from 12-80% of study populations have undergone prior pancreatic resections before TPIAT. This has been shown in multiple studies (particularly a lateral pancreaticojejunostomy or distal pancreatectomy) to have deleterious effects on islet cell harvest, which in turn may confer decreased success of the transplanted beta cell mass (162,117,15). With the earliest reports of TPIAT done in the late 1970s, centers such as the

Table 2: Study Demographics

FACTORS	Minnesota[163]	Leicester[68]	Cincinnati[198]	Cleveland[183]	Arizona^[71]	Alabama^[52]	Baylor *[168]	S. Carolina^[116]
STUDY DATES	1977-2011	1996-2006	2000-2013	2007-2010	2009-2013	2005-2012	2006-2009	2009-2010
NUMBER OF PATIENTS	409	50	112	20	61 (52 TP, 8 CP, 1 partial)	91 (57 TP, 4 CP, 8 DP, 22 whipple)	17	33 (21 TP, 11 CP, 1 DP)
MEAN AGE	35.3	43	37.3	43	42.2	44	40.1	42
BMI	24.5	21	24.2	NR	26.6	23.8	26.1	27
SEX	74% F (303)	52% F (26)	67%F (75)	40% F (8)	63.9% F (39)	54% F (49)	75%F (13)	76% F (25)
FOLLOWUP (median)	NR	8 yrs	74 mo	25 mo	NR (1-24 mo)	19 mo	7.3 mo	9 mo
DURATION of preop narc	3.6 yrs	NR	NR	NR	NR	NR	NR	NR
YEARS of pain or symptoms	9.2	5.4	NR	NR	NR	NR	7	NR
DIABETIC preop	8% (33)	0%	12.5% (14)	NR	0%	NR	5.8% (1)	21% (7)
ETIOLOGY								
Idopathic	41% (168)	48% (24)	75% (84)	55% (11)	73% (45)	NR	53% (9)	24% (8)
Alcohol	7% (29)	36% (18)	2.7% (3)	25% (5)	11% (7)	23% (21)	NR	12% (4)
Divisum	17% (70)	0%	8.9% (10)	10% (2)	0%	NR	NR	9% (3)
Biliary	9% (37)	10% (5)	0%	0%	0%	NR	NR	42% (14)
Genetic	14% (57)	0%	13.4% (15)	10% (2)	16% (10)	NR	NR	9% (3)
Other	12% (49)	6% (3)	0%	0%	0%	0%	47% (8)	3% (1)
PRIOR SURG	21% (86)	12% (6)	38% (43)	25% (5)	80% (49)	25% (23)	17% (3)	54% (18)
Whipple/Beger	6% (25)	6% (3)	20.5% (23)	NR	NR	NR	NR	15% (5)
DP/Duval	8% (33)	6% (3)	7.1% (8)	NR	NR	NR	NR	12% (4)
Puestow/Frey	9% (37)	0%	7.1% (8)	NR	NR	NR	NR	6% (2)
Other	8% (33)	NR	NR	NR	NR	NR	NR	6% (2)

* extrapolated data; ^ studies including partial and total pancreatectomies; *DP*, distal pancreatectomy; *TP*, total pancreatectomy; *CP*: completion pancreatectomy; *NR*, data not reported

University of Minnesota are amassing follow-up data on patients spanning decades, which helps to continually improve treatment for this patient population.

The predominant goal of surgery is mitigation of intractable pain. These centers together **(Table 3)** have demonstrated that TPIAT can successfully alleviate pain in the majority of CP patients (52,68,71,116,162,168,183,198). Nearly all patients undergoing TPIAT are narcotic dependent at the time of surgery and studies show rates of narcotic independence at 1 year postop of 55%-71% (162,68,198,71). This success shows continued improvement over time likely due to the effect of tapering long-term narcotic users. Additionally, these same studies demonstrated significant improvement in pain scores postoperatively when compared to their preoperative state.

The addition of islet autotransplantation to attenuate the otherwise complete insulin and glucagon deficiency is also proving positive. Insulin independence rates range from 10%-47% across studies, though attrition rate increases over time **(Table 3).** The patients who become insulin dependent but retain partial islet function demonstrated by C peptide positivity gain a benefit by ameliorating the potentially severe glycemic swings seen in pancreatogenic diabetes, thus improving diabetes management (14). The centers at Minnesota and Leicester report C-peptide positivity rates of 90% and 100% respectively, demonstrating high success rates in islet autotransplantation (162,68). Additionally, studies have shown that postoperative insulin use did not negatively impact quality of life scores (49).

Table 3: Comparison of study results across centers

FACTORS	Minnesota[163]	Leicester[68]	Cincinnati[198]	Cleveland[183]	Arizona^[71]	Alabama^[52]	Baylor *[168]	S. Carolina^[116]
STUDY DATES	1977-2011	1996-2006	2000-2013	2007-2010	2009-2013	2005-2012	2006-2009	2009-2010
IEQ/kg	3,050	2,245	6,027	3,846	3,048	1,955	5,278	NR
INSULIN	1yr/3yr	5yr	1yr/5yr	at follow-up	1-24 months	at follow-up	at follow-up	1 yr
independent	28%, 30%	10%	38%, 27%	20%	19%	15%	47%	24%
partial	49%, 33%	NR	38%, 35% <20U/d	NR	27% <10U/d	NR	53%	15% < 10U/d
dependent	23%, 37%	NR	24%, 38%	80%	54%	NR	0	NR
INSULIN/DAY preop	NR	0	1	NR	0	NR	NR	NR
INSULIN U/d postop	NR	5 yr: 16 *	5 yr: 18.1	11.6	NR	NR	NR	NR
HbA1c preop	NR	NR	NR	6.04	NR	NR	NR	NR
HbA1 postop	82% < 7.0	NR	5 yr: 6.9	7.72	NR	NR	NR	NR
NARCOTIC INDEPENDENCE	2 yr: 59%	1 yr: 60%, 5yr: 84%	1yr: 55%; 5yr: 73%	30%	1 yr: 71%	NR	35%	23%
PAIN SCORE	SF-36 integrated pain score	VAS	SF-36 BODILY PAIN SCORE.	VAS %mild/mod/sev	SF-36 pain score.	SF McGill Pain	VAS	0-10 scale
preop	54	10 for both	9.3	0% mild, 45% mod, 55% severe	25.2	AP: 25.2, NAP: 23.2	7.8	7
postop	1 yr: 31, 2yr: 30	3 for severity, 2 for frequency	1 yr: 53.2, 5 yr: 59.4	80% mild, 15% mod, 5% severe	1 yr: 57.4	AP: 1 yr 20.1, 2yr 15.2; NAP: 1yr 17.5, 2 yr 12.8	NR	6 mo: 5, 6+ mo: 4
NARCOTIC USE `								
preop (ME/d)	NR	120	118.9	89.2	NR	NR	293	357
postop (ME/d)	NR	62	5 yr: 21.1	78	1 mo: 191	NR	76	128
QOL SCORES	SF-36		SF-36	DASS/PDI		SF-36		SF-12
preop	29 PCS, 38 MCS	NR	NR	see study	NR	30.4 PCS 37.1 MCS	NR	25 PCS, 32 MCS
postop	1 yr: 39 PCS, 47MCS; 2yr: 38 PCS, 49 MCS	NR	1 yr: 92% improved from baseline	79-90% improved across all domains	NR	1 yr: 37.6 PCS 37.9 MCS 2yr: 44.4 PCS 45.5 MCS	NR	1 yr: 36 PCS, 44 MCS
SURVIVAL	1yr: 97%, 5yr: 90%, 20yr: 62%	NR	5yr: 94.6%	NR	NR	NR	NR	NR
MORBIDITY	15%	15%	NR	45%	NR	NR	NR	48%
MORTALITY	1.2%	2%	0%	0%	0%	NR	NR	0
LOS (days)	NR	20	14	12	12.4		NR	NR
OR time (hrs)	NR	8	9.1	NR	NR	5.9	NR	4.1
EBL (mL)	NR	NR	549	NR	NR	413	NR	679
BLOOD TRANSFUSION	NR	NR	33.9%	NR	NR	NR	NR	24%
ISLET HARVEST TME (hrs)	4.5	2-4	NR	NR+	NR	NR	NR	4.6
SPLENIC PRESERVATION	30%	96%	routine splenectomy	NR	routine splenectomy	NR	NR	NR *

extrapolated data, ^ studies including partial and total pancreatectomies; *DP,* distal pancreatectomy; *TP,* total pancreatectomy; *CP:* completion pancreatectomy; *NR,* data not reported; *QOL:* quality of life; *AP:* alcoholic pancreatitis; *NAP:* non-alcoholic pancreatitis; *VAS:* visual analogue scale; *DASS/PDI:* depression anxiety stress scale/pain disability index; *SF-36/12:* short form health survey; *PCS/MCS:* physical component score/mental component score; results without time label specified were reported in original study at "time of follow-up"

11. Postoperative Management

It is important to maintain follow-up with TPIAT patients postoperatively as aspects of their anatomy and physiology may be foreign to centers and practitioners not experienced with this treatment. Avoidance of corticosteroids is paramount to avoid harm to the islets (129). In addition, TPIAT patients with infusion of islets into the liver may have abnormal imaging findings. After infusion, the islets engraft into the hepatic sinusoids. Subsequent blockage of terminal portal vein branches and local insulin release may result in hepatic structural changes (134). This in turn may lead to an increase in echogenicity with a nodular appearance on ultrasound. A UK study

showed 25% of patients to have these characteristics, and were stable at 6 and 12 month imaging. These did not correlate with a significant loss of liver function or increase in insulin requirements (134). These changes have also been reported as seen on MRI and thought to be associated with periportal steatosis (26).

12. Conclusion

Thirty-seven years after the first procedure was performed for chronic pancreatitis, TPIAT is proving to be a safe and effective treatment strategy for this difficult and complex disease process. Growing experience is allowing earlier and improved selection of patients for TPIAT, which may improve their postoperative endocrine function, pain relief, and quality of life. Ongoing research in islet processing, preoperative patient assessment and selection, as well as islet engraftment will likely contribute to refining outcomes for patients in the future.

13. References

1. **Ali NS, Walsh RM.** Total pancreatectomy with islet cell auto-transplantation: Update and outcomes from major centers. *Curr Treat Options Gastroenterol* 12(3):350-358. 2014. PMID: 25053231
2. **Anazawa T, Balamurugan AN, Bellin M, Zhang HJ, Matsumoto S, Yonekawa Y, et al.** Human islet isolation for autologous transplantation: Comparison of yield and function using SERVA/Nordmark versus Roche enzymes. *Am J Transplant* 9(10):2383-2391. 2009. PMID:
3. **Balamurugan AN, Loganathan G, Bellin MD, Wilhelm JJ, Harmon J, Anazawa T, et al.** A new enzyme mixture to increase the yield and transplant rate of autologous and allogeneic human islet products. *Transplantation* 93(7):693-702. PMID: 22318245
4. **Balzano G, Maffi P, Nano R, Zerbi A, Venturini M, Melzi R, et al.** Extending indications for islet autotransplantation in pancreatic surgery. *Ann Sur*g 258(2):210-218. 2013. PMID: 23751451
5. **Balzano G, Piemonti L.** Autologous islet transplantation in patients requiring pancreatectomy for neoplasm. *Curr Diab Rep* 14(8):512. 2014. PMID: 24915889
6. **Bellin MD, Balamurugan AN, Pruett TL, Sutherland DE.** No islets left behind: Islet autotransplantation for surgery-induced diabetes. *Curr Diab Rep* 12(5):580-586. 2012. PMID: 22777430
7. **Bellin MD, Beilman GJ, Dunn TB, Pruett TL, Chinnakotla S, Wilhelm JJ, et al.** Islet autotransplantation to preserve beta cell mass in selected patients with chronic pancreatitis and diabetes mellitus undergoing total pancreatectomy. *Pancreas* 42(2):317-321. 2013. PMID: 23146918
8. **Bellin MD, Blondet JJ, Beilman GJ, Dunn TB, Balamurugan AN, Thomas W, et al.** Predicting islet yield in pediatric patients undergoing pancreatectomy and autoislet transplantation for chronic pancreatitis. *Pediatr Diabetes* 11(4):227-234. 2010. PMID: 19708905
9. **Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al.** Total pancreatectomy and islet autotransplantation in chronic pancreatitis: Recommendations from PancreasFest. *Pancreatology* 14(1):27-35. 2014. PMID: 24555976
10. **Bellin MD, Freeman ML, Schwarzenberg SJ, Dunn TB, Beilman GJ, Vickers SM, et al.** Quality of life improves for pediatric patients after total pancreatectomy and islet autotransplant for chronic pancreatitis. *Clin Gastroenterol Hepatol* 9(9):793-799. 2011. PMID: 21683160
11. **Berney T, Mathe Z, Bucher P, Demuylder-Mischler S, Andres A, Bosco D, et al.** Islet autotransplantation for the prevention of surgical diabetes after extended pancreatectomy for the resection of benign tumors of the pancreas. *Transplant Proc* 36(4):1123-1124. 2004. PMID: 15194391
12. **Bhargava R, Senior PA, Ackerman TE, Ryan EA, Paty BW, Lakey JR, et al.** Prevalence of hepatic steatosis after islet transplantation and its relation to graft function. *Diabetes* 53(5):1311-1317. 2004. PMID: 15111501
13. **Blondet JJ, Carlson AM, Kobayashi T, Jie T, Bellin M, Hering BJ, et al.** The role of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Surg Clin North Am* 87(6): 1477-1501, x. 2007. PMID: 18053843
14. **Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al.** EUS-based criteria for the diagnosis of chronic pancreatitis: The rosemont classification. *Gastrointest Endosc* 69(7):1251-1261. PMID: 19243769

15. **Dorlon M, Owczarski S, Wang H, Adams D, Morgan K.** Increase in postoperative insulin requirements does not lead to decreased quality of life after total pancreatectomy with islet cell autotransplantation for chronic pancreatitis. *Am Surg* 79(7):676-680. 2013. PMID: 23815999
16. **Dunderdale J, McAuliffe JC, McNeal SF, Bryant SM, Yancey BD, Flowers G, et al.** Should pancreatectomy with islet cell autotransplantation in patients with chronic alcoholic pancreatitis be abandoned? *J Am Coll Surg* 216(4):591-596; discussion 596-598. 2013. PMID: 23521936
17. **Farney AC, Najarian JS, Nakhleh RE, Lloveras G, Field MJ, Gores PF, et al.** Autotransplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. *Surgery Aug* 110(2):427-437; discussion 437-439. 1991. PMID: 1858051
18. **Galvani CA, Rilo HR, Samame J, Gruessner RW.** First fully robotic-assisted total pancreatectomy combined with islet autotransplant for the treatment of chronic pancreatitis: A case report. *Pancreas* 42(7):1188-1189. 2013. PMID: 24048458
19. **Galvani CA, Rodriguez Rilo H, Samame J, Porubsky M, Rana A, Gruessner RW.** Fully robotic-assisted technique for total pancreatectomy with an autologous islet transplant in chronic pancreatitis patients: Results of a first series. *J Am Coll Surg* 218(3):e73-78. 2014. PMID: 24559970
20. **Garcea G, Weaver J, Phillips J, Pollard CA, Ilouz SC, Webb MA, et al.** Total pancreatectomy with and without islet cell transplantation for chronic pancreatitis: *A series of 85 consecutive patients. Pancreas* 38(1):1-7. 2009. PMID: 18665009
21. **Giulianotti PC, Kuechle J, Salehi P, Gorodner V, Galvani C, Benedetti E, et al.** Robotic-assisted laparoscopic distal pancreatectomy of a redo case combined with autologous islet transplantation for chronic pancreatitis. *Pancreas* 38(1):105-107. PMID: 19106750
22. **Gruessner RW, Cercone R, Galvani C, Rana A, Porubsky M, Gruessner AC, et al.** Results of open and robot-assisted pancreatectomies with autologous islet transplantations: Treating chronic pancreatitis and preventing surgically induced diabetes. *Transplant Proc* 46(6):1978-1979. 2014. PMID: 25131087
23. **Gustavson SM, Rajotte RV, Hunkeler D, Lakey JR, Edgerton DS, Neal DW, et al.** Islet auto-transplantation into an omental or splenic site results in a normal beta cell but abnormal alpha cell response to mild non-insulin-induced hypoglycemia. *Am J Transplant* 5(10):2368-2377. 2005. PMID: 16162184
24. **Jin SM, Oh SH, Kim SK, Jung HS, Choi SH, Jang KT, et al.** Diabetes-free survival in patients who underwent islet autotransplantation after 50% to 60% distal partial pancreatectomy for benign pancreatic tumors. *Transplantation* 95(11):1396-1403. PMID: 23558506
25. **Jung HS, Choi SH, Kim SJ, Choi DW, Heo JS, Lee KT, et al.** Delayed improvement of insulin secretion after autologous islet transplantation in partially pancreatectomized patients. *Metabolism* 58(11):1629-1635. 2009. PMID: 19604519
26. **Keith RG, Keshavjee SH, Kerenyi NR.** Neuropathology of chronic pancreatitis in humans. Can J *Surg May* 28(3):207-211. 1985. PMID: 3995416
27. **Lee BW, Jee JH, Heo JS, Choi SH, Jang KT, Noh JH, et al.** The favorable outcome of human islet transplantation in korea: Experiences of 10 autologous transplantations. *Transplantation* 79(11):1568-1574. 2005. PMID: 15940047
28. **Lundberg R, Beilman GJ, Dunn TB, Pruett TL, Chinnakotla SC, Radosevich DM, et al.** Metabolic assessment prior to total pancreatectomy and islet autotransplant: Utility, limitations and potential. *Am J Transplant* 13(10):2664-2671. 2013. PMID: 23924045
29. **Marquez S, Marquez TT, Ikramuddin S, Kandaswamy R, Antanavicius G, Freeman ML, et al.** Laparoscopic and da vinci robot-assisted total pancreaticoduodenectomy and intraportal islet autotransplantation: Case report of a definitive minimally invasive treatment of chronic pancreatitis. *Pancreas* 39(7):1109-1111. 2010. PMID: 2086169
30. **Mehigan DG, Bell WR, Zuidema GD, Eggleston JC, Cameron JL.** Disseminated intravascular coagulation and portal hypertension following pancreatic islet autotransplantation. *Ann Surg* 191(3):287-293. PMID: 6767451
31. **Memsic L, Busuttil RW, Traverso LW.** Bleeding esophageal varices and portal vein thrombosis after pancreatic mixed-cell autotransplantation. *Surgery* 95(2):238-242. 1984. PMID: 6420919
32. **Mirkovitch V, Campiche M.** Successful intrasplenic autotransplantation of pancreatic tissue in totally pancreatectomised dogs. *Transplantation* 21(3):265-269. PMID: 781926
33. **Morgan K, Owczarski SM, Borckardt J, Madan A, Nishimura M, Adams DB.** Pain control and quality of life after pancreatectomy with islet autotransplantation for chronic pancreatitis. *J Gastrointest Surg* 16(1):129-133; discussion 133-134. 2012. PMID: 22042566
34. **Morgan KA, Theruvath T, Owczarski S, Adams DB.** Total pancreatectomy with islet autotransplantation for chronic pancreatitis: Do patients with prior pancreatic surgery have different outcomes? *Am Surg* 78(8):893-896. 2012. PMID: 22856498

35. **Najarian JS, Sutherland DE, Baumgartner D, Burke B, Rynasiewicz JJ, Matas AJ, et al.** Total or near total pancreatectomy and islet autotransplantation for treatment of chronic pancreatitis. *Ann Surg* 192(4):526-542. 1980. PMID: 6775603
36. **Najarian JS, Sutherland DE, Matas AJ, Goetz FC.** Human islet autotransplantation following pancreatectomy. *Transplant Proc* 11(1):336-340. 1979. PMID: 109963
37. **Navaneethan U, Venkataraman J.** Recent advancements in the pathogenesis of pain in chronic pancreatitis: The argument continues. Minerva Gastroenterol *Dietol* 56(1):55-63. 2010. PMID: 20190725
38. **Neal CP, Dennison AR, Garcea G.** Surgical therapy in chronic pancreatitis. Minerva *Gastroenterol Dietol* 58(4):377-400. 2012. PMID: 23207614
39. **Ngo A, Sutherland DE, Beilman GJ, Bellin MD.** Deterioration of glycemic control after corticosteroid administration in islet autotransplant recipients: A cautionary tale. *Acta Diabetol* 51(1):141-145. 2014. PMID: 21822910
40. **Ong SL, Pollard C, Rees Y, Garcea G, Webb M, Illouz S, et al.** Ultrasound changes within the liver after total pancreatectomy and intrahepatic islet cell autotransplantation. *Transplantation* 85(12):1773-1777. 2008. PMID: 18580470
41. **Pollard C, Gravante G, Webb M, Chung WY, Illouz S, Ong SL, et al.** Use of the recanalised umbilical vein for islet autotransplantation following total pancreatectomy. *Pancreatology* 11(2):233-239. 2011. PMID: 21577042
42. **Sutherland DE, Bellin MD, Blondet JJ, Beilman GJ, Dunn TB, Chinnakotla S, Pruett TL, Freeman ML, Balamurugan AN, Bland B, Radosevich DM and Hering BJ** (2012). Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Chronic Pancreatitis*. ISBN: 978-953-51-0011-9, InTech, http://www.intechopen.com/books/chronic-pancreatitis/total-pancreatectomy-and-islet-autotransplantation-for- chronic-pancreatitis
43. **Sutherland DE, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, Dunn TB, et al.** Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 214(4):409-424; discussion 424-426. 2012. PMID: 22397977
44. **Sutton JM, Schmulewitz N, Sussman JJ, Smith M, Kurland JE, Brunner JE, et al.** Total pancreatectomy and islet cell autotransplantation as a means of treating patients with genetically linked pancreatitis. *Surgery* 148(4):676-685. 2010. PMID: 20846557
45. **Takita M, Naziruddin B, Matsumoto S, Noguchi H, Shimoda M, Chujo D, et al.** Variables associated with islet yield in autologous islet cell transplantation for chronic pancreatitis. *Proc (Bayl Univ Med Cent)* 23(2):115-120. 2010. PMID: 20396418
46. **Toledo-Pereyra LH, Rowlett AL, Cain W, Rosenberg JC, Gordon DA, MacKenzie GH.** Hepatic infarction following intraportal islet cell autotransplantation after near-total pancreatectomy. *Transplantation* 38(1):88-89. 1984. PMID: 6429912
47. **Vardanyan M, Rilo HL.** Pathogenesis of chronic pancreatitis-induced pain. *Discov Med* 9(47):304-310. PMID: 20423674
48. **Walsh RM, Saavedra JR, Lentz G, Guerron AD, Scheman J, Stevens T, et al.** Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis. *J Gastrointest Surg* 16(8):1469-1477. 2012. PMID: 22673773
49. **Wang H, Desai KD, Dong H, Owzarski S, Romagnuolo J, Morgan KA, et al.** Prior surgery determines islet yield and insulin requirement in patients with chronic pancreatitis. *Transplantation* 95(8):1051-1057. 2013. PMID: 23411743
50. **Wilhelm JJ, Bellin MD, Dunn TB, Balamurugan AN, Pruett TL, Radosevich DM, et al.** Proposed thresholds for pancreatic tissue volume for safe intraportal islet autotransplantation after total pancreatectomy. *Am J Transplant* 13(12):3183-3191. 2013. PMID: 24148548
51. **Wilson GC, Ahmad SA, Schauer DP, Eckman MH, Abbott DE.** Cost-effectiveness of total pancreatectomy and islet cell autotransplantation for the treatment of minimal change chronic pancreatitis. *J Gastrointest Surg* 19(1):46-55. 2014. PMID: 25095749
52. **Wilson GC, Sutton JM, Abbott DE, Smith MT, Lowy AM, Matthews JB, et al.** Long-term outcomes after total pancreatectomy and islet cell autotransplantation: Is it a durable operation? *Ann Surg* 260(4):659-667. 2014. PMID: 25203883
53. **Zureikat AH, Nguyen T, Boone BA, Wijkstrom M, Hogg ME, Humar A, et al.** Robotic total pancreatectomy with or without autologous islet cell transplantation: Replication of an open technique through a minimal access approach. *Surg Endosc* 29(1):176-183. 2014. PMID: 25005012