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Islet Autotransplantation and Total Pancreatectomy

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Introduction

Surgical intervention for chronic pancreatitis may be indicated in patients with incapacitating pain refractory to medical management. The choice of operation reflects assumptions about the underlying mechanism of pain and is based on anatomic circumstances such as duct dilation, duct strictures, intraductal calculi, or the presence of an inflammatory mass. A decompressive procedure such as lateral pancreaticojejunostomy may be appropriate for patients with large-duct disease, in whom the mechanism of pain is presumed to relate to duct obstruction. On the other hand, a pancreatic resection such as pancreaticoduodenectomy may be appropriate for patients with a dominant inflammatory mass in the head of the pancreas. In appropriately selected patients operated in experienced centers, mortality is usually less than 2%, and complete or substantial pain relief can be achieved in approximately 80–90%.

Some patients with refractory painful chronic pancreatitis have no obvious conventional surgical option because they lack a suitable anatomic target for resection or decompression. Others have persistent or recurrent pain despite operative intervention, or incapacitating frequent attacks of acute pancreatitis without other therapeutic options. It is for this subset of patients that total or completion pancreatectomy with or without islet autotransplantation may be a reasonable option.

Total Pancreatectomy and the Introduction of Islet Autotransplantation

Total pancreatectomy for malignant diseases of the pancreas was first reported in 1943 by Rockey[1]. Extended survival was rare. Small series of total pancreatectomy for patients suffering from the intractable pain of chronic pancreatitis began to appear in the 1960s[2]. Although substantial relief of pain was achieved in approximately 60–80% of patients, the procedure was reserved for only the most exceptional clinical circumstances due to the substantial metabolic consequences of both total endocrine and exocrine insufficiency.

Total pancreatectomy leads to complete insulin deficiency (Type 3 diabetes). Glycemic control after TP is notoriously difficult with standard pharmacological insulin therapy due to loss of glucagon-dependent counter-regulation. Complete exocrine insufficiency after total pancreatectomy is also difficult to treat, not only because of the requirement for high dose

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pancreatic enzyme supplementation but also due to imperfect mixing and emptying that is a consequence of the gastro-biliary-enteric reconstruction.

Preservation of islet mass through autologous transplantation of homogenized pancreas was first reported in 1980[3,4]. Complications were significant and included portal hypertension and disseminated intravascular coagulation. Although some islet autograft function was achieved, this approach fell out of favor until advances in isolation and preservation of islets for the purpose of allotransplantation led to renewed interest. Since 1995, an increasing number of centers have reported total pancreatectomy with islet autotransplantation (IAT) [5,6]. In this procedure, the patient's own islets are isolated and infused into the portal vein, where they become engrafted within the hepatic parenchyma without the need for immunosuppression, as would otherwise be required in allotransplantation (Fig. 1).

Patient selection

IAT may be appropriate in a highly selected subgroup of patients with chronic or recurrent acute pancreatitis or patients requiring extensive pancreatic resection for benign disease (Table 1)[6]. Total pancreatectomy leads to complete exocrine insufficiency and a significant possibility of postoperative diabetes even with successful IAT. Therefore, this procedure should be reserved for patients with intractable pain or frequent recurrences of acute attacks who have reached the point of incapacitation and who have no conventional surgical alternative. A lower threshold for intervention may be considered for patients with hereditary pancreatitis syndromes associated with elevated risk of progression to pancreatic cancer, such as is associated with mutations in the PRSS1 gene. IAT is no longer considered experimental and is covered by most third-party payers in the United States.

Contraindications to IAT include pre-existing insulin-dependent diabetes, steatohepatitis or other parenchymal liver disease, and portal vein thrombosis (Table 2). Patients with visceral hyperalgesia, pain symptoms that are more "functional" than "pancreatic" in character, or evidence of psychosocial maladaptation such as drug-seeking behavior are generally poor candidates for total pancreatectomy with or without IAT.

Surgical approach

Pancreatectomy

The pancreatectomy is performed in two stages: first, a distal pancreatectomy (resecting the body and tail with or without the spleen), and second, a pancreaticoduodenectomy (resecting the head and uncinate process together with the duodenum). The procedure is most often performed by open laparotomy, although a robotic-assisted laparoscopic approach has been described [7]. To minimize ischemia to the islet tissue, the gastroduodenal artery and the splenic artery and vein are preserved until just prior to resection. The spleen may be preserved on the short gastric vessels, although occasionally anatomic circumstances are favorable to enable pancreatectomy without sacrificing the splenic artery and vein.

Pancreas processing

After devascularization, the pancreas is promptly removed and placed in cold preservation solution. The duodenum and spleen are separated from the pancreas. The pancreatic duct is

assessed for integrity, cannulated, and flushed with cold preservation solution, and blood is flushed from the major vessels. The organ is then packed in cold preservation solution and transported to the islet isolation laboratory [8]. The goal of islet isolation is to digest the pancreas and disrupt the exocrine pancreatic tissue in order to release relatively pure islets into a small tissue volume that can be safely infused into the portal vein [9]. The pancreas is first distended by intraductal injection of collagenase, followed by gentle mechanical dispersion using the semi-automated Ricordi method, freeing islets from the exocrine tissue [10,11]. At this point, the pellet containing acinar and endocrine tissue is collected and assessed for islet count, viability, purity, and endotoxin content, and a sample is sent for Gram stain followed by microbiology culture. Direct infusion of large amounts of tissue into the portal vein leads to intrahepatic microembolization and inflammation [12, 13]. To prevent this, many islet centers further purify islets from acinar tissue when the pellet volume exceeds 0.25mL/kg body weight [14]. In the setting of IAT for chronic pancreatitis, the pancreas is usually so fibrotic and atrophic that the tissue volume of the preparation is small enough that purification is unnecessary (Fig.2).

Islet infusion

Islets are most often infused into the patient immediately after processing while the patient is still in the operating room with an open laparotomy incision. Alternatively, islets may be cultured and infused post-operatively by a percutaneous approach [15]. Islets are infused into the portal system using a stump of the splenic vein, via direct puncture of the portal, or by cannulation of the umbilical vein [16]. With significant tissue volume infused into the portal vein, elevation of portal pressure may lead to reduction in blood flow and portal vein thrombosis [13]. Because of this risk, heparin anticoagulation is recommended. Portal pressure is monitored closely during the islet infusion and should not exceed 25–27 cm H₂O (18.4–20mmHg) [13]. When pellet volume is less than 20 ml and the liver is healthy, portal pressure usually does not increase substantially. If portal pressure does rise during infusion of a large volume of unpurified islets, the portal infusion should be discontinued and the remaining islets dispersed instead into the peritoneal cavity, or injected into the leaves of the mesentery or omentum, bowel subserosa, gastric submucosa, or intramuscular space [16,17,18]. Although islets transplanted into these alternative sites have been shown to survive in animal models, whether this approach is effective in the clinical setting is unproven [19].

Early post-operative glycemic management

At the time of isolation, islet vasculature is disrupted, and the infused islets are exposed to mechanical, osmotic, and hypoxic stress, leading to up-regulation of pro-apoptotic pathways [20,21]. Early post-transplant, islets rely on diffusion of nutrients and oxygen to the islet core until neovascularization occurs over the first 2–4 weeks [22, 23]. Autotransplanted islets do not resume full function immediately. They require time for recovery and engraftment, and tight glucose control is necessary to protect islets from toxic hyperglycemia [24, 25]. Therefore, intensive insulin therapy is begun immediately after transplantation, initially by continuous insulin infusion, followed by transition to subcutaneous injection. Insulin therapy should be maintained for at least 3 months, weaning

gradually as hypoglycemia appears. A target of hemoglobin A1c level below 6.5% is optimal to minimize hyperglycemic stress on islets [26,27].

Results of Total Pancreatectomy with IAT

The largest series of IAT have been reported by the University of Minnesota, the University of Cincinnati, and Leicester General Hospital [6,28,29]. A review of data from the National Surgical Quality Improvement Program documented a small but significantly higher incidence of major postoperative morbidity for total pancreatectomy with IAT (41%) compared to total pancreatectomy alone (29%) [30]. Specific endpoints of total pancreatectomy with IAT to consider include relief of pain of chronic pancreatitis, islet function and glycemic control, as well as overall improvement in quality of life.

Relief of Pain

Pain relief after total pancreatectomy is usually achieved in well-selected patients, with approximately two-thirds of patients achieving narcotic independence [28,31]. However, the extent and durability of pain relief has been inconsistently documented. A minority of patients, approximately 10–20%, will have persistent or minimally improved symptoms, reflecting uncertainty regarding the true pathogenesis of pain. The quality of the outcomes in published series is undermined because of the number of patients that are lost to follow-up or otherwise not systematically evaluated.

Endocrine function

At 3 year follow up, one-third of patients in the Minnesota series achieved insulin independence; another third of patients have partial graft function defined by positive blood C-peptide. Those who achieved partial graft function required insulin supplementation; however overall glucose control appeared improved, as HgA1c tended to be below 7 in 82%, compared to above 9 in those without endogenous islet function [6]. In long term follow-up, lower HbA1c correlates with a lower risk of secondary diabetic complications. Patients with positive C-peptide are less “brittle”, have fewer episodes of hyper- and hypoglycemia, and report improved quality of life [6,29]. Cincinnati, Leicester, and other centers have published similar results, with insulin independence in 22%–40% of patients [15,28,32]. Islet yield tends to correlate with insulin independence, although there is considerable variability in the reported series. Other factors affecting outcome include islet viability, beta cell functional capacity, and recipient characteristics, particularly the insulin sensitivity of the recipient [5,6]. Islet yield and quality depends on the quality of the pancreas. Advanced parenchymal damage caused by chronic inflammation and fibrosis lowers islet yield [33,34]. Prior pancreatic surgery also reduces islet yield, with an approximately 50% reduction in patients who have had a lateral pancreaticojejunostomy or distal pancreatectomy [6,16]. Islet isolation technique also impacts islet yield; results in experienced centers are more favorable [5,35]. Thus, the metabolic outcome of IAT depends on many factors including patient selection, surgical procedure and islet processing skills. The likelihood of insulin independence correlates with post-transplant C-peptide to glucose ratio 1 month after the procedure [36]. C-peptide after stimulation in MMTT is also a good predictor of beta cell islet mass [6]. More sophisticated measures of beta cell function and

mass have been performed in a subset of islet autograft recipients enrolled in research trials [5, 37]. Intrahepatic islets secrete insulin in a normal pulsatile pattern, similar to beta cells in the native pancreas although at a lesser magnitude [5, 37].

Long-term survival of autografted islets is well-documented. The longest reported period of insulin independence is 18 years, and C-peptide positivity 22 years after 16 years off insulin [6]. While attrition of function does occur with islet autografts, it is much less than that described for islet allografts for type 1 diabetes [38]. No long-term hepatic or metabolic dysfunction has been observed in over 500 autoislet and 500 alloislet transplant patients who received up to three islet infusions, and no islet or pancreatic cancer has been reported [6,39].

Quality of life

Improvement in quality of life measured by standard instruments has been demonstrated in both adult and pediatric populations [16, 40]. Outcomes in patients undergoing total pancreatectomy with IAT for chronic pancreatitis associated with alcohol use have been reported to be significantly worse than other indications [41]. After total pancreatectomy, patients require lifelong pancreatic enzyme supplementation (usually 96,000 lipase units with each meal) and are advised to follow a low-fat diet. Daily multivitamins including iron and calcium supplementation are also recommended.

Candidates for total pancreatectomy with IAT should be counseled thoroughly. Setting of realistic expectations should be a priority for preoperative discussions. In essence, the patient will be “trading” one disease (the pain of pancreatitis) for another (the endocrine and exocrine consequences of pancreatectomy). Late recidivism of similar or new pain occurs in approximately 15% of patients and is probably underreported. Readmissions for various non-specific abdominal complaints that may be related to narcotic-bowel syndrome, narcotic withdrawal, or exocrine insufficiency may lead to recurrent or persistent narcotic use and abuse.

Special considerations

Pediatric patients

Children undergoing IAT are reported to have higher rates of insulin independence and normalized quality of life compared to adults. Overall 55% of children achieve insulin independence and a further 30% have partial islet function [6]. Success in this group is largely driven by children below age 12, who more frequently require once daily or no insulin therapy compared to teenagers [6]. Whether these favorable outcomes are due to the young age of the patient and the extent of pancreatic disease or to the intrinsic characteristics of young beta cells, or both, is unclear. Young children receive greater numbers of islets for body weight and have lower insulin demands. In addition, beta cells from younger patients also have greater replicatory capacity than adults [42]. In some young patients with severe chronic pancreatitis, islet neogenesis of ductal origin has been observed [43]. Durability of islet function is especially good for young individuals less than 21 years of age and for those with short history of pancreas disease. Most of the patients who maintain excellent islet

function 3 year after the transplant will remain off insulin for years despite their growth and development into adulthood.

Malignancy

In general, IAT is contraindicated for patients with malignant or pre-malignant pancreatic lesions. Parenchymal processing for islet harvest precludes proper histological evaluation and thus staging of pancreatic cancer. Because some acinar and ductal tissue is co-transplanted with the islets, there is at least a theoretical risk of seeding occult cancer cells into the liver. Nevertheless, some islet autotransplants have been reported in patients with localized pancreatic cancer [44, 45]. Although the use of total pancreatectomy for main duct intraductal pancreatic mucinous neoplasm (IPMN) is increasing, simultaneous IAT is generally ill-advised in this setting. Transplantation of islets contaminated with even dysplastic ductal cells risks intrahepatic recurrence of neoplasia and the inability to determine whether malignant transformation of the IPMN had occurred is a distinct disadvantage [5]. Nevertheless, 2 cases of pancreatectomy with IAT in IPMN patients without subsequent recurrence of tumor have been reported [46].

Future directions

Although IAT represents a substantial technical advance, there is still opportunity for improvement at each stage of the procedure. Early referral to an experienced center may allow earlier identification of potential candidates for IAT, in order to limit progressive damage to the pancreas incurred by delay of intervention or by unnecessary surgical procedures that otherwise compromise the outcome of IAT. Optimization of the technique of islet isolation will increase yield and preserve function of autotransplanted islets. Effective method of islet separation from dysplastic or cancerous ductal epithelial elements may extend indications for IAT. Also needed are better strategies to improve islet engraftment, minimize beta cell apoptosis, and prevent damage from innate immunity and inflammation. Peritransplant anti-TNF agents and IL-1 blockade appear promising [47]. A multicenter trial targeting CXC Ligand 8 to inhibit chemotaxis of polymorphonuclear leukocytes has recently been launched [48]. Although intraportal islet transplantation is still the gold-standard for clinical islet autotransplantation, there are theoretical disadvantages including greater glucolipotoxicity and toxin exposure due to the direct contact with portal blood. Intraportal islets may also elicit a rapid endovascular mediated inflammatory reaction [49, 50]. Alternative transplant sites and encapsulation technology are also important areas for future investigation.

Summary

The goal of islet autotransplantation is the preservation of beta cell mass at the time of pancreatectomy. The majority of recipients have significant endogenous beta cell function with positive blood C-peptide after surgery even if only approximately one-third will achieve insulin-independence. In appropriately selected patients, total pancreatectomy combined with IAT achieves relief of pain and improves quality of life with relatively easier-to-manage glycemic control and avoidance of hyper- and hypo-glycemic episodes.

Current research is focused on improving techniques of islet isolation and engraftment as well as long-term survival of autografted islets.

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Key Points

1. Total pancreatectomy with islet autotransplantation may be indicated for adult and pediatric patients with intractable symptoms of chronic or recurrent acute pancreatitis that lack conventional surgical alternatives. Small duct chronic pancreatitis and hereditary pancreatitis syndromes are the most successful settings in which this approach has been applied.
2. Preservation of pancreatic endocrine function by autotransplantation of islets via the portal vein may improve postoperative glycemic management and, in approximately one-third of patients, achieve insulin-independence.
3. Although pain is relieved and quality of life are improved in at least two-thirds of appropriately selected patients, the threshold and optimal timing of total pancreatectomy with islet autotransplantation remain controversial.
4. After total pancreatectomy, careful management of diet with attention to adequate replacement of pancreatic enzymes is important to prevent steatorrhea, malabsorption, and malnutrition.
5. Total pancreatectomy with islet autotransplantation for patients with suspected premalignant or malignant disease of the pancreas is not currently recommended.

Transplantation of Native Islets for Patients with Pancreatitis

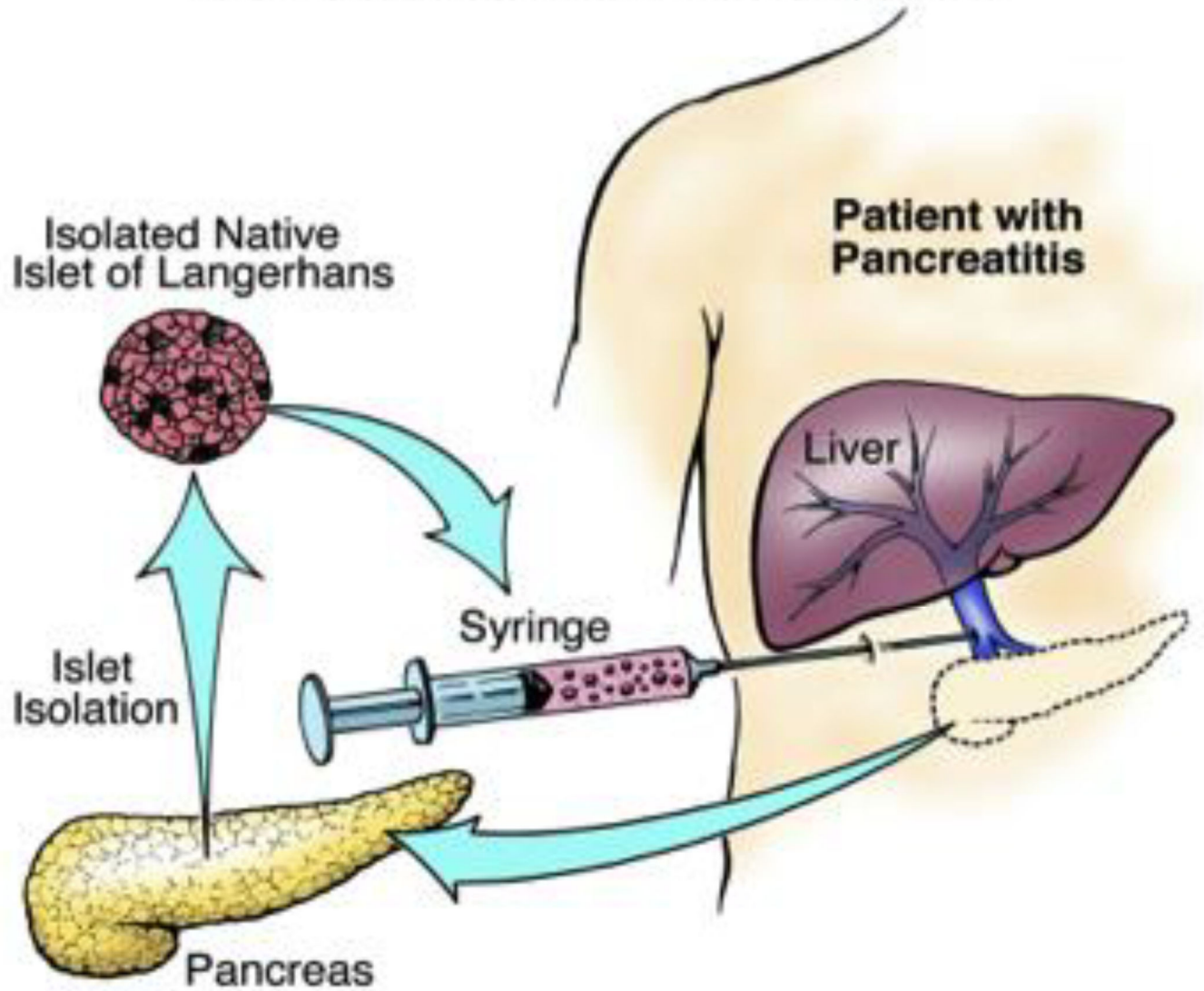


Fig 1.
Transplantation of islets in patients with chronic pancreatitis.

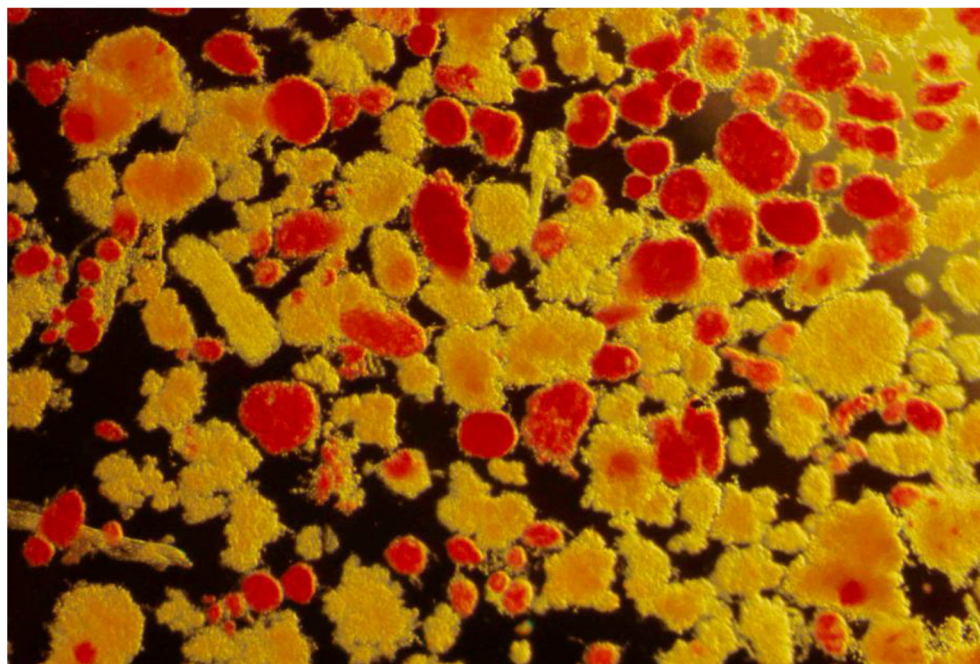
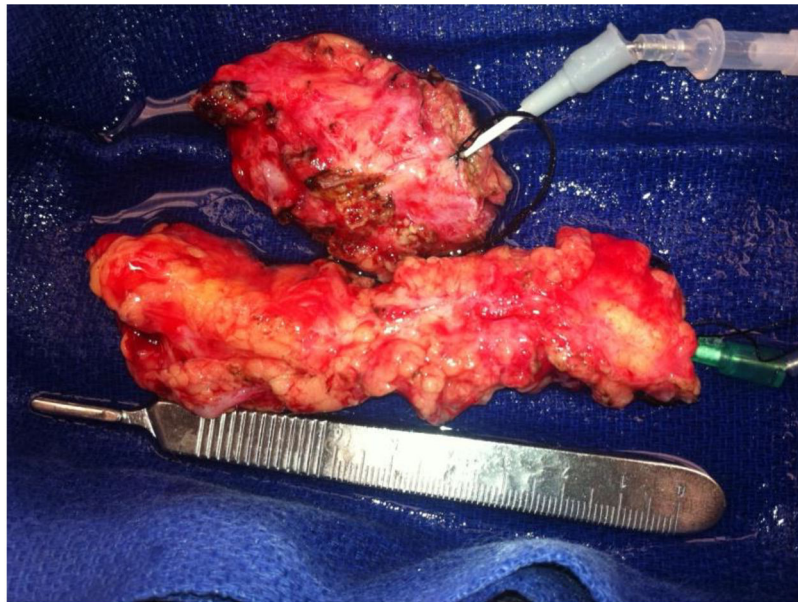


Fig 2.
A) Excised pancreas (a head and a body with tail) from a patient with chronic pancreatitis. Pancreatic duct is cannulated with angiocath allowing for subsequent perfusion with collagenase and organ digestion. B) View of the tissue after pancreas digestion seen in light microscopy. Islets stained with dithizone are in red and acinar tissue remains unstained in yellow-brown. (Magnification 30 \times).

Table 1

Possible Indications for Total Pancreatectomy with Islet Autotransplantation

Small duct chronic pancreatitis
Idiopathic or genetically-linked recurrent acute pancreatitis
Hereditary chronic pancreatitis with cancer risk
Failure of conventional surgery for chronic pancreatitis
Extensive pancreatectomy for trauma or benign pancreatic pathology

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Table 2

Relative Contraindications for Total Pancreatectomy with Islet Autotransplantation

Pre-existing type 1 or type 3 diabetes
Steatohepatitis
Portal vein thrombosis
Portal hypertension
Prior lateral pancreaticojejunostomy
Visceral hyperalgesia
Psychosocial maladaptation

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