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No Islets Left Behind: Islet Autotransplantation for Surgery-Induced Diabetes

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Abstract

For patients with severe chronic pancreatitis refractory to medical interventions, total pancreatectomy can be considered to relieve the root cause of pain. The goal of a simultaneous islet autotransplant is to prevent or minimize the otherwise inevitable surgical diabetes. Islet autotransplant can successfully preserve some endogenous islet function in the majority of recipients, which mediates protection against brittle diabetes. Most maintain reasonably good glycemic control, while 30-40% successfully discontinue insulin therapy. With islet autotransplants reaching a wider clinical audience, refinements in islet isolation techniques and strategies to protect islet grafts post-transplant may further improve the success of this procedure.

Keywords

pancreatitis; chronic pancreatitis; islet transplant; autotransplant; C-peptide; pancreatectomy; diabetes mellitus; beta cell; alpha cel; surgery

Introduction

Chronic pancreatitis is a disease with many etiologies and many treatments. There often comes a time when therapy no longer relieves the chronic pain and discussion of pancreatic extirpation is undertaken. Total pancreatectomy alone results in complete insulin deficiency and associated sequelae. At the time of total pancreatectomy (TP), islet autotransplantation (IAT) can decrease the insulin insufficiency morbidity of the operation [1-8].

Patients afflicted with chronic pancreatitis present with abdominal pain, and have inflammation and fibrosis on pancreatic histopathology [9-11]. The disease is often

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progressive, with escalating pain, potential progression to endocrine and exocrine insufficiency, and an elevated lifetime risk of adenocarcinoma [12]. Initial treatments for chronic pancreatitis include avoidance of alcohol and pancreatic irritants, cholecystectomy for biliary stones or sludge, if present, endoscopic pancreaticobiliary duct decompression, narcotic analgesics, pancreatic enzymes to reduce pancreatic stimulation, antioxidants and celiac plexus or nerve blocks [13-15]. When medical management and endoscopic interventions fail or there is a clear anatomic etiology, surgical management is considered to relieve pain and restore quality of life [9]. However as the repertoire of surgical procedures is broad with quite erratic clinical responses, our philosophy has evolved such that total pancreatectomy and islet autotransplantation is offered to patients with chronic pancreatitis who do not respond to adequate endoscopic duct drainage and medical management. The University of Minnesota patient population includes a significant subset of patients that have failed prior surgical duct drainage or pancreatic resections. Total pancreatectomy results in complete insulin and glucagon deficiency, leaving the patient with surgery-induced insulin-dependent diabetes mellitus, often labile or difficult to safely achieve glycemic control. The goal of an islet autotransplant is to salvage as much of the beta cell mass as possible, in order to preserve endogenous insulin secretion, and either prevent surgical diabetes or minimize the magnitude of such diabetes. In this procedure—an *auto*logous islet transplant--the patient's own islets are isolated and infused into a tributary of the portal vein, without any need for immunosuppression.

Most islet autotransplant procedures are performed in the context of total (or partial) pancreatectomy for chronic pancreatitis or familial/genetic pancreatitis. However, this procedure has been utilized less commonly for other benign pancreatic disease including trauma and benign pancreatic lesions requiring extensive (60-80%) pancreatectomy [16-21]. Because some acinar and ductal tissue is co-transplanted with the islets, islet autotransplant should be avoided if pancreatectomy is performed for malignancy of the pancreas.

Technical aspects of islet isolation

The pancreatectomy is most often performed by open laparotomy, although a robotic-assisted laparoscopic approach has been described [22, 23]. The major technical goal is to preserve the blood supply to the pancreas until removal, to minimize ischemia of the islet tissue. After devascularization, the pancreas is quickly removed placed in cold preservation solution. It is inspected and prepared (removal of duodenum and spleen, pancreatic duct assessed for integrity and gross blood flushed from vessels) and packaged for transport to the islet isolation lab in cold tissue preservation solution. The goal of islet isolation is to digest the pancreas and disrupt the exocrine pancreatic tissue [24], to release relatively pure islets in a small tissue volume which can be safely infused into the portal vein. The pancreas is first distended by intraductal injection of a collagenase enzyme, and then gentle mechanical dispersion using the semi-automated method of Ricordi frees the islets from the exocrine tissue as much as possible [25, 26]. Because high tissue volume increases the risk for portal pressure elevation during islet infusion [27, 28], if the tissue volume is large (>~0.25 mL/kg), the islets can be purified by gradient separation method to reduce volume [29]. Use of customized density gradients, rather than fixed standard purification gradients, can minimize the loss of islets during the purification step [24]. Often, tissue volume is small and the autologous islet preparation can be transplanted unpurified. The number of islets are quantified as islet equivalents (IEQ), which is islet mass standardized to an islet size of 150 micrometers diameter [30].

For autologous islet transplant, islets are most often returned to the patient fresh (not cultured) while the patient is in the operating room with an open incision. Alternatively, islets may be transplanted post-operatively by percutaneous approach [6]. The islets are

infused into the portal system using a stump of the splenic vein, or alternatively direct puncture of the portal or cannulation of the umbilical vein can be used [31]. While the portal site for infusion is most common, islets can be transplanted elsewhere, including the peritoneal cavity, bowel subserosa or submucosa, omental, or intramuscular [1, 31, 32]. With significant tissue volume infused into the portal vein, elevation of portal pressure can be a limiting element. Significant elevations in portal pressures are associated with marked reduction in blood flow and risk for subsequent portal thrombosis [28]. Because of this risk, routine heparin anticoagulation is utilized which in combination of acute portal hypertension elevates the incidence of perioperative bleeding. Minimizing tissue volume infused and thereby minimizing portal pressure elevations reduces bleeding risk. At our institution, when tissue volume is reduced to <0.25 mL/kg and change in portal pressure does not exceed 25 cmH_20, the risk of clinically significant bleeding is <8% [28].

It should be emphasized that patients are receiving their own islets. No immunosuppression is required during or after islet infusion. Thus, islet autotransplant recipients do not have the long-term risks of infection and other immunosuppression side effects that are a consideration in type 1 diabetic recipients receiving islet *allo*grafts from cadaveric pancreatic donors, and islet engraftment and function is not impacted by agents such as tacrolimus and rapamycin which are necessary for islet *allo*grafts but may be detrimental to graft vascularization and beta cell function [33, 34].

Islet isolation, engraftment, and the early post-operative period

At the time of islet isolation, islet vasculature is disrupted, the islets are exposed to mechanical, osmotic, and hypoxic stress, and pro-apoptotic pathways are upregulated [35, 36]. In the early post-transplant period, islets are reliant on diffusion of nutrients and oxygen to the islet core until neovascularization is complete, a process that takes at least 2-4 weeks [37, 38]. In animal models, rates of beta cell apoptosis in the first month post-transplant are very high, and worsened under hyperglycemia, so care is taken to maintain strict glycemic control during the early post-transplant period [39-42]. At our institution, we initiate an insulin drip in the immediate post-operative period to target blood sugar 100-120 mg/dL, followed by transition to subcutaneous insulin at ~1 week post-operatively to target blood sugars 80-125 mg/dL. Post-operative insulin management protocols vary by institution. At the University of Minnesota, we maintain patients on insulin therapy for at least 3 months post-transplant (unless hypoglycemia is present) and then wean as tolerated to maintain long-term goals of fasting blood sugar <126 mg/dL, post-prandial blood sugar <140-180 mg/dL, and hemoglobin A1c level <6.5% (and ideally in normal range for insulin independent patients). Near euglycemia is targeted, to minimize hyperglycemic stress on the beta cell mass which could otherwise contribute to attrition of the beta cell mass over time [43, 44].

Long-term metabolic benefits of preserving endogenous beta cell function

The largest series in islet autotransplantation published are from University of Minnesota, University of Cincinnati, and Leicester [2, 4, 8]. Overall, one-third of patients in the Minnesota series achieve insulin independence, but the majority have islet graft function, as documented by C-peptide positivity (Figure 1) [4, 8]. Cincinnati, Leicester, and other centers have published similar results, with 22%-40% of patients insulin independent [2, 5, 6]. The number of islets transplanted is an important prognostic factor, although there is much overlap between outcomes by islet mass--- some patients with high islet mass will never come off insulin while some with low islet mass do achieve insulin independence. There are many factors that likely mediate this difference—islet viability, beta cell functional capacity, and recipient characteristics, particularly the insulin sensitivity or

insulin requirements of the recipient may all be important factors. Nevertheless, receiving a high islet mass generally conveys a favorable prognosis. Of those patients in the Minnesota series who received >5000 IEQ/kg at the time of transplant, 65-72% were insulin independent at 2-3 years post-transplant. This is in contrast to 12-15% of recipients with <2500 IEQ/kg transplanted [8]. Other factors associated with insulin independence include lack of a prior pancreatic surgery (particularly a partial pancreatectomy or lateral pancreaticojejunostomy) [8, 31] and higher C-peptide to glucose ratio at 1 month post-transplant [45]. The impact of prior pancreatic surgery can be quite dramatic, with an approximately 50% reduction in islet yield in patients who have had a lateral pancreaticojejunostomy (Puestow) or distal pancreatectomy (Table 1).

While attrition of insulin independence does occur with islet autografts, it is much less than that classically described for islet allografts for type 1 diabetes mellitus. In one analysis, of those islet autograft recipients who achieved insulin independence, three quarters maintained insulin independence for 2 or more years [46]. The rate of attrition relates to the initial islet mass; few patients resume insulin in the first several years post-transplant when the initial islet mass was high (>5000 IEQ/kg), but return to insulin use is much more rapid if islet mass was low (<2500 IEQ/kg) [47]. Insulin independence with euglycemia has been documented for 16 years, with graft function for over 2 decades [48] (and unpublished data).

It is important to emphasize that with islet autotransplant, the goal is good glycemic control without brittle diabetes. When insulin independence can be achieved, this is an important bonus, but minimizing the impact of post-surgical diabetes (short of insulin independence) is considered a success. By this standard, most pancreatectomy recipients benefit from an islet autograft. Ninety percent of patients in the Minnesota series and 100% of those in the Leicester series are C-peptide positive after the procedure [4, 8]. Most patients maintain glycemic control within a range recommended by the American Diabetes Association, with 82% of all recipients maintaining an average HbA1c level <7.0% [8]. When islet mass transplanted is high (>5000 IEQ/kg), 100% are C-peptide positive and 94% maintain a HbA1c <7.0% [8].

Ability to predict the number of islets before pancreatectomy is performed is currently limited. Preliminary evidence suggests that metabolic testing by intravenous glucose tolerance tests, arginine stimulation tests, or maximal stimulated arginine may provide a useful surrogate for islet count [48]. In children, body weight and fasting blood sugar were predictive in one small series [49]. When a prior distal pancreatectomy or a surgical drainage procedure such as Puestow or Frey has been performed, islet yield is frequently low, and history of such procedures confer a poor prognosis for the patient in regards both to islet number and insulin independence [8]. In one small series, greater evidence of chronic pancreatitis pathology on CT imaging, by endoscopic retrograde cholangiopancreatography (ERCP), or on endoscopic ultrasound (EUS) was associated with lower islet yield (<5000 IEQ/kg vs >5000 IEQ/kg) [50], and at the same center, body mass index (BMI) >23 kg/m2 is associated with better islet yield [51], although one would suspect that obese patients are also more likely to have high insulin demands/insulin resistance. Severe histopathologic changes on pancreatectomy biopsy characterized by severe fibrosis, acinar atrophy, and inflammation were associated with low islet yield in children and adults [10, 11]. However, it is important to note that islet isolation technique can also impact islet yield [52], and as we improve our isolation protocols, these relationships between predictors and islet isolation results may change.

Children and TPIAT

Although most islet autotransplant procedures have been performed in adults, children with severe chronic pancreatitis are also candidates for the procedure. Unlike adults who often have idiopathic pancreatitis, children frequently carry genetic mutations which predispose them to develop pancreatitis, including mutations in the cationic trypsinogen gene (PRSS1), thepancreatic secretory trypsin inhibitor (SPINK1), or the cystic fibrosis transmembrane conductance regulator (CFTR). While the procedure is essentially the same as in adults, children as a group have higher rates of insulin independence and normalization of quality of life. Overall 40-50% of children achieve insulin independence [31, 53]. This is largely driven by the youngest group of patients, <12 years of age, who more frequently come off insulin or require only once daily basal insulin therapy than their teenage counterparts [53]. The youngest two patients in the Minnesota series, both 5 years of age, have been off insulin for 4 and 7 years (Bellin, unpublished data).

Whether these outcomes are driven by the young age of the recipient, the intrinsic characteristics of the young beta cells, or both is unclear. The young children are smaller, often receive a greater islet number for body weight, and have lower insulin demands, all of which could be favorable for islet engraftment. However, beta cells from younger patients also have greater replicatory capacity than adult beta cells, particularly in children younger than 10 years of age, as found in autopsy studies of non-diabetic children [54]. In some young patients with severe chronic pancreatitis, islet neogenesis of ductal origin has been observed [55]. Since autologous preparations are relatively impure, some ductal tissue is frequently co-infused with the islets. Whether any beta cell replication or neogenesis can take place after transplant is entirely theoretical and has not been documented in clinical islet transplant.

Assessing beta and alpha cell function after TPIAT

Hemoglobin A1c, fasting glucose, and simple C-peptide levels can be routinely measured in clinic. We have observed higher stimulated C-peptide secretion in response to a mixed meal test with greater transplanted islet mass [8]. Mean stimulated C-peptide after 6 mL/kg (max 360 mL) Boost HP is significantly higher in patients with >5000 IEQ/kg vs those with 2500-5000 IEQ/kg or <2500 IEQ/kg ($p<0.001$, unpublished data). However, fasting C-peptide does not distinguish between these three groups.

More sophisticated measures of beta cell function and mass have been performed in a subset of islet autograft recipients enrolled in research trials. In 6 recipients studied longitudinally (at mean of 6 years post-transplant), half of islet autotransplant recipients exhibit a reduction over time in insulin secretion in response to intravenous glucose, while insulin secretory reserve as measured by glucose potentiated arginine stimulation generally remained stable [48]. In this study, glucose dispersal rate correlated with the number of islets transplanted. Glucose potentiated insulin response may be the best estimate of functional beta cell mass post-transplant, although the acute insulin response to glucose or arginine also correlate reasonably well with transplanted islet mass [56]. Intrahepatic islets secrete insulin in a normal pulsatile pattern, similar to that of the beta cells in the native pancreas although at a lesser magnitude [57]. Compared to islet allografts for type 1 diabetes-- which are subject to immunity and drug toxicity-- islet autografts exhibit about twice as much function per islet transplanted at 1-4 years post-transplant, as measured by insulin secretion on intravenous glucose tolerance tests and glycemic control by oral glucose tolerance test [58].

Whether alpha cells can mount a normal glucagon response to hypoglycemia following islet transplantation is less clear. Intraportal islet transplants produce glucagon normally in response to an injection of arginine, demonstrating the presence of alpha cells in the

transplanted islet graft. However, Kendall et al demonstrated that glucagon responses were absent in response to hypoglycemia [59]. This may be mediated by the location of the islet graft. In diabetic dogs undergoing islet autotransplantation, glucagon production was similarly absent when islets were transplanted to the liver, but glucagon counter-regulation did occur when islets were transplanted into the peritoneal cavity [60]. Zhou et al. proposed that intrahepatic glucose flux related to glycogenolysis in the liver suppresses the ability of the alpha cell to recognize systemic hypoglycemia, thus resulting in defective glucagon counter-regulation [61]. Anecdotally, we have islet transplant recipients who report hypoglycemia even off insulin therapy, although the timing is most often post-prandial and less often fasting.

Opportunities for improvement, recent research, and future directions

While islet autotransplantation is successful in many cases, opportunities for improvement exist. Strategies that improve isolation outcomes, improve islet engraftment, prevent damage from innate immunity and inflammation, or minimize beta cell apoptosis represent potential strategies to increase the proportion of insulin independent patients or long-term survival of the islet graft. Refinements to collagenase and neutral protease solutions used for isolation and customization of pancreatic tissue density gradients for COBE purification have improved the yield and recovery during islet isolation [24, 52], and such improvements in islet isolation are likely to continue. Other ongoing studies are investigating agents that may protect the islets from stress or reduce beta cell apoptosis [62], or minimize the impact of innate inflammatory or thrombotic impact on the islet graft immediately post-transplant.

Additional research is ongoing with regards to the hepatic site for transplantation. Although intraportal islet transplantation is still the gold-standard for clinical islet autotransplantation, there are theoretical disadvantages including greater gluco-lipotoxicity and toxin exposure due to the direct contact with the portal blood. Intraportal islets may also elicit an instant blood mediated inflammatory reaction [63, 64], although the clinical significance in heparin treated clinical islet autotransplant recipients is unclear. Peritoneal transplants have been used as a second site in patients who could not receive all islets in the liver at our institution, and do function comparably in animal models. Recently, Rafeal et al reported successful outcome after forearm intramuscular islet transplant in a child [32], and mice data suggest superior revascularization, comparable to that seen in native pancreatic islets [65]. Thus, future studies may identify a site that has superior short and long-term outcomes compared to the liver. In the meantime, intraportal infusion continues to be the standard of care.

Conclusions

Total pancreatectomy is a major surgical intervention that should not be entertained lightly, but a spectrum of benign pancreatic diseases is best treated with this procedure. The goal of islet autotransplantation is to preserve as much beta cell mass as possible at the time of pancreatectomy, most often performed for chronic pancreatitis. Ninety percent or more of recipients have endogenous beta cell function (as documented by C-peptide positivity) after surgery and in 4 of 5 patients glycemic control is maintained within the goal range for diabetes mellitus. With a high islet mass transplanted, stimulated C-peptide is higher, HbA1c more frequently in goal range, and insulin independence more common; however, even some patients with a low mass islet graft will maintain normal blood sugars off insulin therapy, highlighting the potential for success with even a small number of islets under the right conditions. Current research is directed at improving the islet isolation process and the engraftment and long-term survival of the islet graft, directed to further improve our ability to prevent post-operative diabetes mellitus with this procedure.

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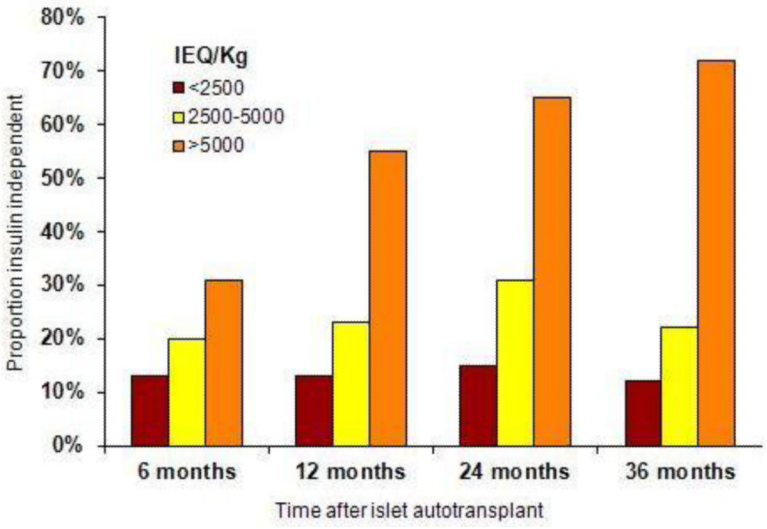

Figure 1.
Insulin independence by islet yield and duration after islet transplant in autograft recipients at the University of Minnesota (Data from Sutherland et al. [8].)

Table 1

Relationship between the history of pancreatic surgery and islet yield in 413 isolation procedures

Pancreatic Surgery	Islet Yield (IEQ/kg, mean ± SD)
No direct pancreatic surgery	3794 ± 2242
Whipple	3647 ± 1672
Berger/ Frey	2654 ± 2151
Distal pancreatectomy	1973 ± 2028
Puestow	1883 ± 1853

Data from Sutherland et al. [8].