Total pancreatectomy and islet autotransplantion for chronic and recurrent acute pancreatitis

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Purpose of review
We reviewed the current state of total pancreatectomy with islet autotransplantation (TPIAT) for chronic pancreatitis and recurrent acute pancreatitis (RAP).

Recent findings
An increasing number of centers in the United States and internationally are performing TPIAT. In selected cases, TPIAT may be performed partially or entirely laparoscopically. Islet isolation is usually performed at the same center as the total pancreatectomy surgery, but new data suggest that diabetes outcomes may be nearly as good when a remote center is used for islet isolation. Ongoing clinical research is focused on patient and disease factors that predict success or failure to respond to TPIAT. Causes of persistent abdominal pain after TPIAT may include gastrointestinal dysmotility and central sensitization to pain. Several clinical trials are underway with anti-inflammatory or other islet protective strategies to better protect islets at the time of infusion and thereby improve the diabetes results of the procedure.

Summary
In summary, there is an increasing body of literature emerging from multiple centers highlighting the benefits and persistent challenges of TPIAT for chronic pancreatitis and RAP. Ongoing study will be critical to optimizing the success of this procedure.

Keywords
acute pancreatitis, chronic pancreatitis, diabetes, islet autotransplant, total pancreatectomy

INTRODUCTION

Total pancreatectomy with islet cell autotransplantation (TPIAT) is a complex surgical procedure performed to eliminate the pain of pancreatitis and mitigate the severity of resultant pancreatogenic diabetes mellitus. In the islet autotransplant (IAT) portion of the procedure, the patient's own islets are isolated from the resected pancreas and infused into the liver. Because it is an autologous transplant, no immunomodulatory drugs are required (Fig. 1) [1,2]. The procedure was first performed at the University of Minnesota in 1977 for chronic pancreatitis. Over the past decade, increased awareness of the surgical technique and improved quality of life for patients after surgery has led to increased utilization of TPIAT as a treatment for patients with chronic pancreatitis and/or recurrent acute pancreatitis (RAP) with refractory disease despite appropriate medical and endoscopic therapy [1,3]. An increasing number of centers are performing this procedure in the United States, and internationally, including in the United Kingdom and, recently in Australia for a child with hereditary pancreatitis [4,5,6,7,8▪,9]. Although chronic pancreatitis and RAP remain the primary indications for TPIAT, expanding indications for the procedure include abdominal trauma requiring partial or total pancreatectomy, and, more controversially, for selected patients with pancreatic tumors or malignancy requiring a total or completion pancreatectomy [10–12]. The latter is not currently done in the United States. The present review will focus on the current state of TPIAT for chronic pancreatitis and RAP. In this review, we will highlight recent advances and updates on the technical aspects of the surgical procedure and islet isolation, quality of life outcomes, pain relief, diabetes

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KEY POINTS

- Although quality of life on average is improved after TPIAT, current research focuses on identifying factors that limit success after the procedure and identifying patients who are likely to benefit.
- Gastrointestinal dysmotility and central sensitization of pain are recently recognized as factors likely contributing to persistent abdominal pain syndromes after TPIAT.
- Factors that have recently been associated with better diabetes outcomes include young age at surgery, whereas pancreatic calcifications and intrapancreatic fat have been associated with less favorable metabolic results.
- Ability to restore insulin independence after TPIAT has been limited by loss of islets resulting from isolation stress, hypoxia, and inflammatory response to infusion, and several clinical trials are ongoing to protect the islets at time of infusion from these detrimental factors.

outcomes, and research and strategies to improve the success of the procedure.

REVIEW OF RECENT LITERATURE

Surgical and islet isolation techniques

Since the first TPIAT was performed, there have been advances in the clinical and basic science that have impacted the technical approaches to total pancreatectomy and islet isolation and infusion.

Updates on the technical aspects of total pancreatectomy

The traditional approach to TPIAT has consisted of an open procedure to perform the total pancreatectomy, partial duodenectomy, and restoration of continuity of the gastrointestinal and biliary systems (Roux-en-Y duodenojejunostomy and choledochojejunostomy, respectively). Recent advances in the surgical approach include utilization of laparoscopic, laparoscopic-assisted, or robotic TPIAT in selected cases [13–17]. A laparoscopic approach to TPIAT (LTPIAT) appears to be well tolerated and feasible, with a 10% rate of converting to an open procedure in a recent case series, with difficult anatomy from previous surgery cited as the typical reason for conversion [13]. Patients undergoing LTPIAT may have a shorter length of stay and decreased need for prokinetic agents in the postoperative period [18▪]. Further research is needed to establish the long-term benefit and safety of LTPIAT over the open approach, and to determine which patients are appropriate candidates.

Even with open TPIAT, there is a risk that the procedure will need to be completely aborted for technical reasons. In a recent series of 110 patients, in 10 cases TPIAT could not be completed, most commonly because of adhesions complicating resection of the pancreas or severe bleeding. This

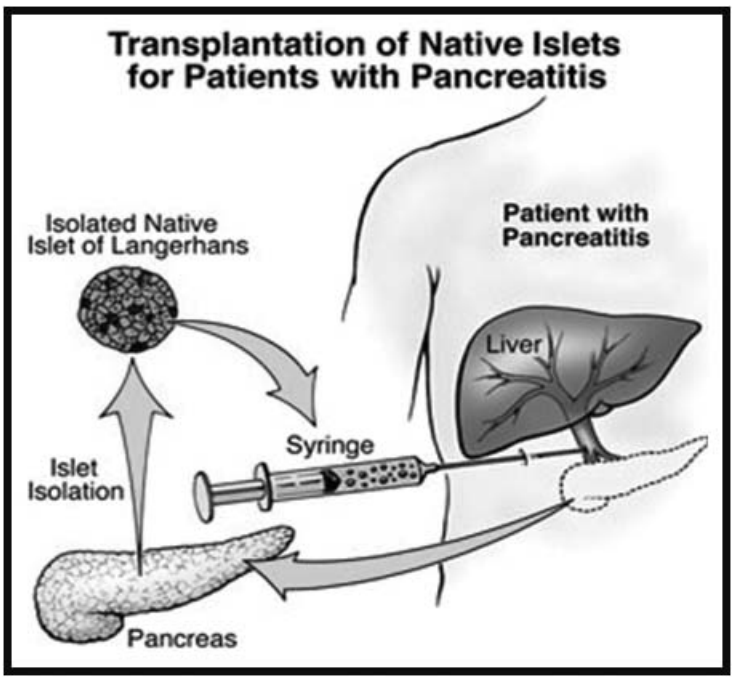

FIGURE 1. Schematic of pancreatectomy with intraportal islet infusion, adapted from Bondet *et al.* [2].

risk of aborted procedure was associated with higher BMI, male sex, and prior pancreas surgery or Endoscopic retrograde cholangiopancreatography with stenting [19].

Updates on the technical aspects of islet isolation

Avoiding prolonged cold ischemia time of the pancreas is critical to the successful isolation of viable and functional islets. Surgical technique for TPIAT aims to minimize ischemia time first through delayed ligation of pancreatic blood supply [1]. However, after the pancreas is isolated from the patient, it must undergo processing in a specialized laboratory for islet isolation prior to autotransplantation. Transport to the lab, islet isolation, and transport back to the patient contribute to cold ischemia time of islets. Although islet isolation facilities are most often located at the center performing the surgery ('local' isolation), remote isolation using a facility at a different institution has been reported. Remote isolation by necessity involves a longer ischemic time for the pancreas, but this short period of cold ischemia may not have a detrimental effect on the islet isolation results [20]. In a recent large series of TPIAT recipients, insulin independence did not differ in those who received islets from a local or remote islet isolation facility, although hemoglobin A1c level and C-peptide levels after TPIAT were somewhat better in those individuals who received islets isolated at a local facility [21▪▪].

Supernatant from the islet product and pancreatic preservation solution are routinely cultured for microbial contamination and are frequently positive for bacterial growth. In one recent large series, more than half of patients had a positive culture from one or both of the pancreas preservation solution and final islet product [22]. This is not surprising as these are diseased pancreata, which have often been exposed to prior endoscopic procedures, stenting, and/or prior surgery. Data from both a large adult and pediatric series both found no significant clinical impact of having a positive culture, if patients were appropriately treated with perioperative antibiotics [22,23]. Patients did not have increased risk of clinical infection [22], and there was no adverse impact on diabetes outcomes, when key variables including islet mass transplanted were considered in the analysis [23]. In contrast, one small series of 27 TPIAT recipients found an association between poor metabolic outcomes and bacterial colonization of the islet product; in this series, the patients with positive islet cultures also had a lower islet yield available for transplant, and so whether there was a causal relationship between bacterial colonization and outcomes or whether colonization was a marker of more severe pancreatic injury (and hence impaired islets) is unclear [24].

QUALITY OF LIFE AND PAIN OUTCOMES

TPIAT has been shown to improve quality of life (QOL) and reduce the need for opioids for patients with chronic pancreatitis, patients with RAP, and in specific subgroups of patients such as young children and patients with genetic pancreatitis [1,3,25▪▪,26,27,28,29▪,30]. Metrics for assessment of QOL include the short form 12 (SF-12) and SF-36 surveys, in addition to others. Pain outcomes are frequently measured in terms of morphine equivalent units, or simply a qualitative assessment of whether or not patients continue to require opioid medications after TPIAT. Some patients will not benefit from TPIAT, however [9,31]. One focus of ongoing multicenter collaborative research is to identify which patient and disease factors predict improved QOL and narcotic independence after TPIAT, in order to improve patient selection and preoperative counseling [8▪].

Single center studies have suggested potential predictors of pain relief and improved QOL after TPIAT, and also potential risk factors for failure. Patients with refractory RAP appear to benefit from TPIAT when endoscopic and medical treatment options are exhausted [3,32]; although further comparison to chronic pancreatitis is needed, one might hypothesize that those patients with relapsing pancreatitis and pain-free intervals may be less susceptible to central sensitization, a suspected cause of persistent postoperative pain [33]. Sub-populations that have potentially more complete response to TPIAT include genetic forms of pancreatitis and young children [25▪▪,29▪,34]. Although major surgery should always be approached with appropriate caution in a very young child, it is notable that in one series of 16 children ages 3–8 years old undergoing TPIAT, pain relief and withdrawal of opioids was observed for all 16 children, along with a higher insulin independence rate than described for older children and adults [25▪▪]. These data are important for pediatricians' and pediatric gastroenterologists' to be aware of when considering timing of surgical consultation, although long-term data are needed as these children transition to adolescence and adulthood.

Identifying risk factors for TPIAT failure is even more critical, in order to avoid TPIAT in those patients unlikely to benefit. In a clinical series of more than 500 patients at a single center, Chinnakotla *et al.* [35] observed an independent association of more than three previous pancreatic stents, diagnosis of pancreas divisum, and obesity (BMI $\geq$30 kg/m^2) with persistent pancreatic pain at 1 year

post-TPIAT. There is also an increasing body of literature to suggest that, despite resolution of pancreatic pain after TPIAT, some patients are at risk of developing a new type of abdominal pain that limits their opioid independence [32]. Larger comparative studies are needed to delineate the cause of and risk factors for this new pain. Development of gastroparesis and central sensitization have both been suggested as potential sources of new pain syndromes [18▪,31]. Delayed gastric emptying (DGE) is a known complications of pancreaticoduodenectomy [18▪,36], and it is estimated that up to 35% of patients who undergo TPIAT develop some degree of persistent DGE, which may be lessened (at least early after surgery) by LTPIAT [37]. In one small study, patients with symptoms of gastrointestinal dysmotility after TPIAT also had reduced QOL scores thus highlighting the potential detrimental impact of this complication [18▪].

DIABETES OUTCOMES

Most patients undergoing TPIAT do not have diabetes before surgery. In undergoing total pancreatectomy, therefore, not only are patients subjected to surgical complications, but they also risk a labile form of diabetes if IAT is not successful. In this sense, optimizing diabetes outcomes is imperative to 'do no harm' in the process of alleviating pancreas pain. Transplanted islet cell mass is the most consistent predictor of short-term and long-term islet graft function [1,26,27,35]. Prior pancreatic surgery, impaired glycemic control before surgery, and longer duration of disease are all risk factors for lower islet mass transplanted and may be important to consider when counseling the patient and considering timing of intervention [1,29▪,38–40].

Other factors have been associated with favorable or poor diabetes outcomes including age of the patient at time of TPIAT, pancreas morphology on imaging, and intrapancreatic fat. As previously noted, in one small series, children age 3–8 years undergoing TPIAT had a higher rate of insulin independence than that observed in older patients; 80% were insulin independent at least for some time after surgery, but long-term follow up is ongoing to determine the longevity of insulin independence in this cohort [25▪▪]. For children and adults with hereditary pancreatitis because of mutations in the serine protease-1 (*PRSS1*) gene, the islet mass isolated for transplant and likelihood of insulin independence both decrease with age and duration of disease (Fig. 2), corresponding to a 13% reduction in islet mass for every 5 years of age and a 22% reduction for every 5 years of diagnosed disease before TPIAT [29▪]. However, as a whole, patients with genetic disease, including *PRSS1,* cystic fibrosis transmembrane receptor mutations, or other pancreatitis-associated genetic mutations, overall have similar diabetes outcomes as those without identified genetic risk factors [27,41].

Preoperative cross-sectional imaging may also identify patients at high risk for low islet mass and persistent insulin dependence after TPIAT.

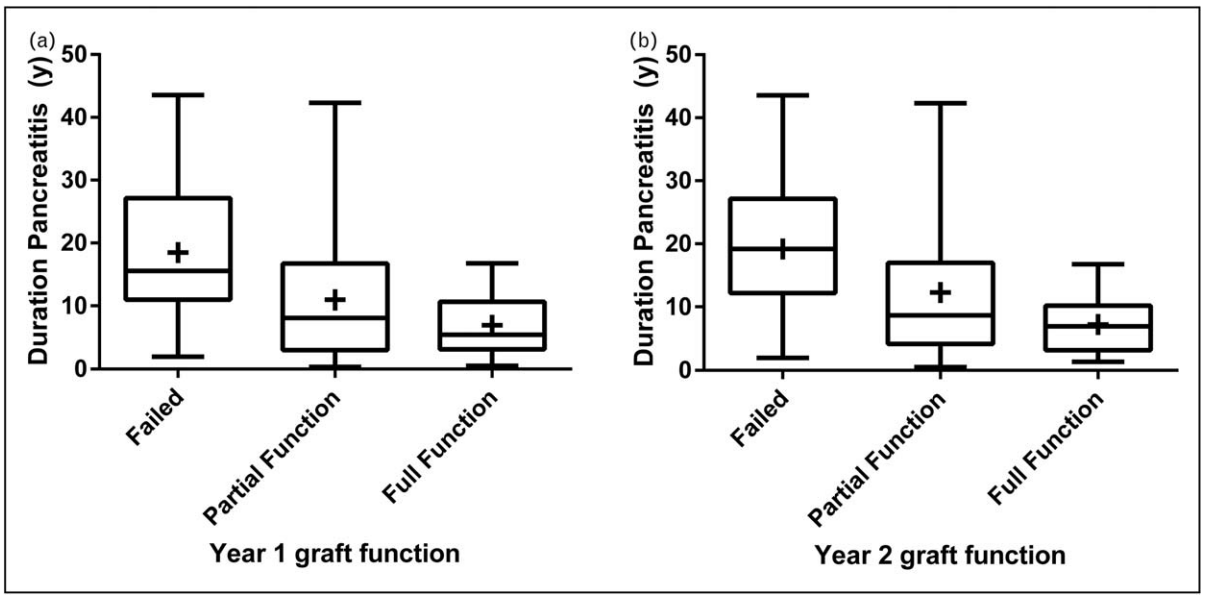

FIGURE 2. The relationship between islet graft function and duration of diagnosed pancreatitis in patients with the *PRSS1* gene. In this figure, full islet graft function is insulin independence, partial function is C-peptide levels at least 0.6 ng/ml postprandial but requiring insulin treatment, and islet graft failure is C-peptide less than 0.6 ng/ml or in the absence of C-peptide data, patient requires multiple daily insulin injections. Adapted with permission [29▪].

Reduced measured pancreas volume, calcifications, duct dilation, and atrophy all correlate with lower islet mass and worse diabetes outcomes; the presence of pancreatic calcifications conveys a particularly high risk for a poor diabetes outcome, associated with a four-fold increased risk of persistent insulin dependence after TPIAT compared to those with noncalcific disease [42]. In addition, increased pancreatic fat content noted on gross examination by the islet isolation team has been recently associated with poor diabetes outcomes. Patients with higher intrapancreatic fat content were less likely to be insulin independent and had higher postprandial glucose levels at 1 year after TPIAT despite a similar islet mass isolated for transplant, when compared to a matched control group with low intrapancreatic fat content [43]. One hypothesis is that intrapancreatic fat may contribute to β-cell dysfunction and thereby convey poor outcomes after TPIAT.

Although most attention has focused on hyperglycemia and diabetes after TPIAT, on the opposite side of the spectrum, hypoglycemic episodes can restrict lifestyle and impair quality of life for some TPIAT recipients. Exercise-induced hypoglycemia is common following TPIAT, and may be because of a deficiency in endogenous glucose production during moderate exercise when compared with healthy controls [44,45▪]. Hypoglycemia following a high-carbohydrate meal has also reported to occur in insulin independent patients after TPIAT, and may result from altered gastrointestinal anatomy and a deficient glucagon response to falling blood glucose [46▪]. Although TPIAT recipients have normal basal levels of glucagon, an impaired glucagon counter-regulatory response to hypoglycemia appears to be specifically related to use of the liver as a site for islet infusion [44]. Research is ongoing to better understand the mechanisms underlying hypoglycemia after TPIAT, and how to best prevent the occurrence of hypoglycemia, including the potential utility of alternate sites for islet transplant.

Finally, advances in diabetes technologies may provide opportunities to improve the care and the quality of life for those individuals who do continue to require insulin after TPIAT. For example, in one small pilot study, closed-loop insulin pump technology was able to maintain postoperative blood glucose levels in target range better than traditional insulin injections, without an increase in hypoglycemia episodes [47]. Similarly, as continuous glucose monitoring technology continues to improve, such approaches may minimize the need for frequent fingerstick blood glucoses while still allowing for accurate monitoring of blood glucose levels [48,49].

PROTECTING ISLETS DURING TRANSPLANTATION AND PROMOTING ISLET ENGRAFTMENT

Transplanted islets are subject to cell death from the moment of isolation and infusion into the recipient, mediated partially by β-cell apoptosis resulting from isolation stress and hypoxia, and exacerbated by the instant blood mediated inflammatory reaction (IBMIR) that is elicited when islets are infused into the portal vasculature [50–53]. Limiting these processes has been the object of recent investigation; however, targeting such complex mechanisms has proven challenging.

One recent area of investigation centered on pharmacologic approaches to increase the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) by blocking the enzyme dipeptidyl peptidase 4 (DPP-4) that metabolizes endogenous GLP-1 and GIP. However, when nondiabetic patients with TPIAT were randomized to receive a DPP-4 inhibitor (sitagliptin) or placebo after islet infusion in a double-blinded study, no difference was observed for insulin independence, insulin dose, or islet function between the two groups suggesting no benefit on islet engraftment or survival with this class of medication [54]. More recently, various medications have been under study to target IBMIR, as this inflammatory and thrombotic reaction to intraportal islet infusion is known to cause β-cell death [50]. Promising agents currently in clinical study include cytokine blockade with TNFα, IL-1, or IL-8 inhibitors, and a more generalized anti-inflammatory and anti-apoptotic approach with α-1 antitrypsin [55–60]. In addition, cotransplantation of mesenchymal stem cells with islets has improved islet survival in rodent and nonhuman primate studies and is under early study in clinical TPIAT recipients [61–64].

One challenge in this area of research has been an inability to directly measure islet loss in clinical IAT. Biomarkers to track β-cell loss during islet isolation and transplantation are needed as a metric for the effectiveness of islet protective strategies. Unmethylated insulin DNA is one potential marker of β-cell death, which was shown to be elevated early after TPIAT and correlated with glycemic outcomes 90 days after TPIAT [65]. Another potential β-cell biomarker, microRNA 375, has been inversely correlated with postdigestion islet count, as well as insulin requirements and C-peptide levels, and other outcomes measures [66,67].

CONCLUSION

In conclusion, TPIAT has been increasingly utilized as a treatment for refractory chronic pancreatitis and RAP. With the growth of TPIAT, less invasive

approaches to the surgery and innovations in islet isolation, including remote isolation, are being explored. Some patients clearly benefit more than others in the resolution of pain, improved quality of life, and diabetes outcomes after TPIAT but ongoing research is needed to validate patient and disease features that predict success. Loss of islet mass after TPIAT remains a problem, but optimistically, this limitation may be surmountable with islet protective strategies including anti-inflammatory medications.

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Conflicts of interest

M.B. has received research support in TPIAT from: Dompe Pharmaceuticals, Medtronic, Merck. M.B. has also served in the past 3 years on medical advisory boards for NovoNordisk, AbbVie, and ARIEL Precision Medicine.

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