HHS Public Access

Author manuscript

Ann Surg. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Ann Surg. 2015 January ; 261(1): 21–29. doi:10.1097/SLA.0000000000001059.

Total Pancreatectomy With Islet Autotransplantation:

Summary of an NIDDK Workshop

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Abstract

A workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases focused on research gaps and opportunities in total pancreatectomy with islet autotransplantation (TPIAT) for the management of chronic pancreatitis. The session was held on July 23, 2014 and structured into 5 sessions: (1) patient selection, indications, and timing; (2) technical aspects of TPIAT; (3) improving success of islet autotransplantation; (4) improving outcomes after total pancreatectomy; and (5) registry considerations for TPIAT. The current state of knowledge was reviewed; knowledge gaps and research needs were specifically highlighted. Common themes included the need to identify which patients best benefit from and when to intervene with TPIAT, current limitations of the surgical procedure, diabetes remission and the potential for improvement, opportunities to better address pain remission, GI complications in this population, and unique features of children with chronic pancreatitis considered for TPIAT. The need for a

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Disclosure: The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

multicenter patient registry that specifically addresses the complexities of chronic pancreatitis and total pancreatectomy outcomes and postsurgical diabetes outcomes was repeatedly emphasized.

Keywords

chronic pancreatitis; islet transplantation; pain; pancreatectomy; pancreatic exocrine insufficiency

Total pancreatectomy with islet autotransplantation (TPIAT) was first performed in 1977 for management of chronic pancreatitis (CP).[1] In this procedure, the pancreas is completely resected to remove the visceral source of pain, and the islets are transplanted back into the patient, most typically via infusion into the portal vein, to reduce the risk of postsurgical diabetes mellitus.[2] Although utilization of TPIAT in the treatment of CP has increased during the past decade, many questions remain about who is an appropriate candidate, when to intervene, how to perform the procedure itself, and how to improve the proportion of patients who are free of pain and diabetes after the procedure. Moreover, standardization of presurgical assessment and follow-up, and multicenter outcomes data are largely lacking.

For this reason, the National Institute of Diabetes and Digestive and Kidney Diseases convened a workshop entitled “Total pancreatectomy with Islet Auto-Transplantation: Gaps, Needs, and Opportunities” on July 23, 2014 at the University Club in Pittsburgh, PA. The purpose of the workshop was to bring together experts in TPIAT from the various academic centers performing this procedure to identify key areas of need for future research.

Nineteen speakers participated in the workshop. The program was divided into 5 sessions: (1) patient selection, indications, and timing; (2) technical aspects of TPIAT; (3) improving success of islet autotransplantation; (4) improving outcomes after total pancreatectomy; and (5) registry considerations for TPIAT. In addition, Food and Drug Administration (FDA) regulatory requirements for islet isolation were presented. The current state of knowledge was reviewed, and knowledge gaps research needs were specifically highlighted. The sections in the following text summarize the key elements of each session, and identify priority areas for future research.

PATIENT SELECTION, INDICATIONS, AND TIMING OF TPIAT

Overview of the Problem

TPIAT is most often utilized in patients with painful and debilitating CP who have not responded to medical, endoscopic, and/or surgical therapies and whose impairment in quality of life (QoL) due to pain is substantial enough to accept the risk of developing postoperative insulin-dependent diabetes and a lifelong commitment to pancreatic enzyme replacement therapy (PERT). Although a recent systematic review reported significant reductions in narcotic use after TPIAT in 2 studies[3] and a large cohort study of 409 patients reported that 59% were free of narcotic use at 2 years,[4] pain outcomes have been variable and not uniformly assessed across most studies.

The only published criteria for patient selection for TPIAT have been set forth from the University of Minnesota[4] (Table 1); these rely on the ability of imaging studies, pancreatic

function tests, or histopathology to detect pancreatic fibrosis. However, advancing age, alcohol use, smoking, diabetes, and obesity can cause pancreatic atrophy, fatty degeneration or fibrosis in those who have chronic abdominal pain due to etiologies other than CP.[5–7] In addition, chronic narcotic use for pain can lead to narcotic bowel syndrome[8] and central sensitization of pain,[9–11] both of which can be difficult to diagnose and treat, and adversely impact the outcomes after pancreatic surgery,[12] including TPIAT. Thus, limitations in diagnostic testing and difficulty in distinguishing pancreatitis from other sources of pain complicate the selection of candidates. In addition, there are emerging limited data suggesting that pain responses might be better in those patients with CP with genetic mutations[13] compared to those who are alcoholics.[14] The risks of insufficient islet mass and central sensitization of pain along with the likelihood of progression of disease should be considered in the timing of intervention.

Before considering TPIAT, the initial treatment of patients who have CP is focused on mitigating their unrelenting or recurring abdominal pain.[15,16] Patients who imbibe alcohol or smoke should stop. Smokers with *PRSS1* should be strongly encouraged to quit because of exponentially elevated risk of pancreatic cancer. In some patients, pancreatic enzyme supplementation may reduce pain or pancreatitis attacks. Nonnarcotic analgesics should be tried first, but many need narcotic analgesics. Some patients need escalating doses, with the addition of analgesic patches. Neuromodulators are often prescribed by pain clinics. Percutaneous or endoscopic celiac ganglion blocks can be tried but rarely give substantial or permanent pain relief, and transient responses often cannot be repeated.[15,16]

Patients who require narcotic analgesics, with or without complete relief, are candidates for invasive procedures in an attempt to remove or modify the underlying cause of the pain.[17] Selection of the best therapy for CP is based frequently on physician experience and suffers from a paucity of robust high-level evidence. Options include endoscopic retrograde cholangiography (ERCP) with stenting of strictures and stone removal if present, pancreatic head resection (Whipple), or lateral pancreaticojejunostomy without (Puestow) or with pancreatic head resection (Frey, Beger), with the latter procedures reserved for those with a dilated main pancreatic duct. Importantly, these procedures have been associated with variable success[18–22] but have never been compared head-to-head with TPIAT.

ERCPs have mixed value; improvement in pain is usually fairly prompt because there is no recovery period as from surgery. The goal should be eradication of any strictures and removal of main duct stones.[17,23] Because previous surgical drainage procedures (Puestow or Beger) compromise islet yield if a subsequent TPIAT is done,[4,24,25] 1 paradigm is to do any indicated drainage procedures primarily by endoscopic methods, with limited use of traditional surgical drainage. Surgical drainage might be considered over TPIAT for select patients with dilated main pancreatic duct who are already diabetic, poor candidates for a major resection procedure such as TPIAT, have a history of alcoholism, or are assessed not to be suitable to handle the consequences of possible diabetes and pancreatic insufficiency. TPIAT presents a potentially successful approach for small-duct CP where few other treatment options exist; genetic or hereditary etiologies may be particularly appropriate for TPIAT over other surgical approaches, but the most appropriate timing for intervention even for genetic disease remains unclear.

CP presents a significant economic burden, requiring a disproportionately high volume of medical resources compared to other health conditions.[26] Although TPIAT has been performed for during 30 years in the United States and for 20 years in Europe, the evolution of health care systems—and particularly the way highly specialized procedures are funded—has focused attention upon complex surgical procedures and their cost-effectiveness including TPIAT. Demonstrating the cost-effectiveness of TPIAT will be essential for financial coverage of TPIAT, and for minimizing financial barriers to access. The main issues relate to the direct costs of the procedure, the health economic impact (total health costs plus economic impact) of the disease, and the cost savings of successful abrogation of CP by TPIAT.[27] The high operating costs of an islet autotransplant facility are similar in Europe and the United States after allowing for cost-of-living differences and staffing costs, and a comprehensive analysis of TPIAT undertaken in the United Kingdom demonstrated the cost-effectiveness of this procedure.[28] Such analyses are lacking in the United States.

Research Gaps and Opportunities

Research priorities should focus on devising simple and accurate criteria for diagnosing noncalcific CP, determining which patients are most likely to benefit from TPIAT, and the timing of intervention. Pain assessment and quality-of-life (QoL) instruments need to be standardized for use in this patient population across all TPIAT centers so that results can be reported and compared in a consistent manner. Randomized controlled trials of TPIAT versus other surgical approaches or ERCP are not likely to be feasible. Rather, comprehensive registry measures focusing on important outcomes including persistent pain, nutritional metrics, and diabetes are critical to compare TPIAT with other procedures, and to determine which prognostic factors best predict outcomes to identify which patients are appropriate candidates.

Specific priorities for research in this population include:

- Advances in diagnostic testing that distinguish earlier stage CP from other conditions that cause abdominal pain.
- Better definition of preoperative measures, which select patients most likely to benefit from TPIAT.
- Development of metrics to determine ideal timing for intervention, both to preserve islet mass and to optimize pain and QoL outcomes.
- Investigation of the role of psychological comorbidities, cognitive behavioral therapies, and medical comorbidities.
- Development of measures of pain, including those for central sensitization of pain such as quantitative sensory testing.
- Cohort studies and comprehensive registry mechanisms to compare TPIAT with other treatments for CP, including repeated ERCP and surgical interventions.
- Assessment of the impact of repeated ERCP procedures on TPIAT outcomes, including impact on islet mass and risk of microbial contamination of the islet

preparation; a “step-up” approach with repeated ERCPs could be contrasted with a “top-down” approach of earlier TPIAT.

- Determination of safety and cost-effectiveness of newer surgical techniques, including laparoscopic or robotic approaches to TPIAT.
- Determination of the cost-benefit of TPIAT in the United States.

TECHNICAL ASPECTS OF TPIAT

Overview of the Problem

TPIAT is a complex procedure with profound long-term effects for patients with debilitating pain from CP. The goals of TPIAT are to maximize improvements in patient QoL and to optimize islet isolation and long-term function. Technical considerations in TPIAT include a discussion of optimal surgical management, best islet isolation techniques, and ideal islet engraftment conditions.

A multidisciplinary approach to preoperative patient preparation is an essential component of success. Patient education is necessary to set realistic patient expectations, with specifics of hospital course, postoperative recovery, potential complications, and difficulties of narcotic weaning. Patients must understand the significant implications of long-term diabetes and exocrine pancreatic insufficiency (EPI). Physiologic preoperative preparation is important as well, including nutritional optimization.

During pancreatectomy, techniques to minimize warm ischemia time are central to operative conduct. Ligation of the splenic and gastroduodenal arteries is delayed until the final steps of the procedure. Immediate placement of the pancreas in cold balanced electrolyte solution, along with exsanguination of the organ by flushing the arterial vessels and opening the venous outflow can potentially improve islet survival. The spleen is preserved selectively as this may affect warm ischemia time.

Gastrointestinal (GI) reconstruction is undertaken with consideration of the conditions specific to the patient with CP. Roux-en-Y reconstruction is preferred to avoid bile reflux and afferent limb problems in these patients with a high prevalence of gastroparesis. Enteral feeding tubes are used in those patients at risk for postoperative nutritional deficiencies.

Heparin is administered at the time of intraportal islet infusion (although protocols vary, an initial bolus of 70 units per kg is commonly used). Portal venous pressures are measured at multiple points during infusion because elevated pressures greater than 30 mm Hg correlate with the development of portal vein thrombosis.[29] Moderate anticoagulation after autotransplantation is employed with consideration of postoperative bleeding risk.

Prevention of surgically induced diabetes and effective glucose control after TPIAT depend largely on the mass and quality of islets isolated from the diseased pancreas. The process of isolating islets from normal human pancreas from cadaveric donors has been established for more than 2 decades[30] and is essentially followed in TPIAT with slight modifications. The isolation process primarily consists of enzymatic digestion of the tissue followed by separation of islets from excessive acinar tissue using density gradient centrifugation.

Obtaining consistent islet yields from CP pancreata remains a technical challenge due to the variability in gross morphology of the pancreas and structural changes due to CP. The success of the islet isolation primarily relies on the efficient delivery of an optimal dose of collagenase enzymes into the pancreatic tissue. Alterations in pancreatic ductal structure, calcification in ducts, and accumulation of fibrotic layers in the pancreatic parenchyma can significantly hinder enzyme perfusion. Enzyme quality, perfusion time, ductal pressure, and temperature affect islet yield. Significantly higher islet yield per gram of pancreas has been obtained by adjusting the dose of collagenase enzymes according to the severity of fibrosis and age of the donor.[31] A new enzyme mixture of collagenase and neutral proteases has been proposed to improve both islet yield and viability.[32,33] Secondary purification is performed only in select cases when a large volume of pancreatic digest is obtained. Assessment of exocrine tissue and islet density is important for the selection of an optimal density gradient range for islet purification. Despite these recent advances, mean islet yields in CP cases remain significantly less than with cadaveric donor pancreata, indicating the need for further refinement of the process.

The intraportal site remains the most common site for islet infusion in TPIAT, primarily because it is the most well studied and infusion is generally well tolerated. However, during the islet infusion process, approximately 50% of transplanted islets are lost. Intravascular infusion of islets triggers a severe, nonspecific inflammatory response—immediate blood-mediated inflammatory reaction (IBMIR)—which is responsible for much of the islet loss.[34] Engraftment of the surviving islets is further compromised by the relatively hypoxic environment of the portal venous system. Kupfer cells and hyperglycemia are additional stressors to the newly transplanted islets. These limitations inherent in the liver site have led to consideration of alternative transplant sites. Multiple alternative sites that may provide metabolic and immunologic benefits have been identified in animal models and some are now being evaluated for clinical use.[35,36] Ideal properties of an alternative implantation site include sufficient oxygen tension, minimal IBMIR, and accessibility for implantation. Sites that have been evaluated include renal subcapsule, testicle, thymus, omentum,[37] muscle,[38] small intestinal submucosa, and bone marrow.[39]

Research Gaps and Opportunities

Opportunities for improvement of current techniques in pancreatectomy, islet isolation, and islet engraftment are abundant. Specific research priorities include the following:

- Standardization of preoperative patient selection and education protocols.
- Improved intraoperative techniques to further minimize islet warm ischemia time.
- Improved operative techniques that maximize long-term GI absorptive function, motility, and nutrition.
- Determination of best perioperative patient care strategies, including minimizing fluid and narcotic administration and alternative antiemetic and analgesic therapies to enhance recovery.
- Studies to advance islet isolation techniques, including novel enzymatic combinations and delivery methods that may enhance islet recovery.

- Minimization of islet loss in the peritransplant period, including therapies to limit IBMIR.
- Well-designed trials of multiple infusion sites for islet autotransplantation beyond the liver, in animal models and human clinical studies to better understand the propriety of various potential implantation sites. This may include bone marrow, muscle (with scaffolding), gut submucosa, and omentum.
- Biotechnology approaches to islet protection including islet encapsulation or scaffold devices.

IMPROVING SUCCESS OF ISLET AUTOTRANSPLANTATION

Overview of the Problem

Pancreatic islet transplantation has been proven a valid approach in treating diabetes (allotransplantation) and preventing surgically induced diabetes after pancreatectomy (autotransplantation). Multiple studies have been focused on understanding reasons for islet loss and/or altered functionality. Having identified some of the mechanisms behind islet loss and graft failure, different strategies should be adopted to improve pancreatic islet transplantation outcomes.

Nondiabetic patients with CP have a higher likelihood of insulin independence after TPIAT when a greater islet mass is transplanted, with more than 60% of recipients of an islet graft more than 5000 islet equivalents per recipient body weight (IEQ/kg) achieving insulin independence.[4] However, the variability in outcomes for any islet mass transplanted is great. Nearly 40% of patients with a high islet mass graft (>5000 IEQ/kg) are insulin dependent, whereas up to 15% of those with marginal to low islet mass (<2500 IEQ/kg) are insulin independent 2 years after TPIAT. One critical factor contributing to this finding is variability in the engraftment and survival of islet grafts. It has been estimated that 30% to 60% of the islets that are infused may be lost.[40] From research studies, we can identify some of the factors that mediate this islet loss.

β-Cell apoptosis is induced by the isolation procedure and persists in the early posttransplant period, exacerbated by other islet stressors such as hypoxia and hyperglycemia. Uncontrolled hyperglycemia increases the number of islets needed to reverse diabetes[41]; thus adequate insulin treatment in the postoperative period is critical. When islets are infused, the exposure of the islets and surface tissue factor to the blood induces a procoagulatory and proinflammatory cascade. This has been demonstrated in clinical TPIAT recipients with an increase in thrombin–antithrombin complexes and reduction in platelets in the 3 hours after the procedure, and an increase in proinflammatory cytokines IL-6 and IL-8 in the first week after islet infusion.[34] In addition, late and altered revascularization is known to occur after islet infusion.[42] Even when insulin independence can be sustained, long-term attrition of the islet graft is observed. Endoplasmic reticulum stress has been proposed,[43] and islet amyloidosis, which is observed in primate[44] and human alloislet grafts.[45]

TPIAT should be performed before pancreatic islet functionality is compromised. Even if diabetes is not evident before TPIAT, islet functionality should be investigated before performing the procedure. Oral (mixed meal test) and intravenous (arginine, glucose) secretagogues have been used in this population. Oral stimulatory testing (mixed meal test or an oral glucose tolerance test) is easy to perform in the clinical setting but lacks linear correlation with islet mass.[46] The most informative β-cell function study is glucose potentiation of arginine-induced insulin/C-peptide secretion. Intravenous arginine is the ideal stimulatory test for β-cell function. It can be effectively used for patients who may have impaired fasting glucose,[47,48] whereas intravenous glucose itself, the more conventional secretogogue, has poor utility in patients whose fasting glucose is more than 100 mg/dL and is ineffective when the fasting glucose is more than 115 mg/dL.[49] Moreover, glucose potentiation of arginine-induced insulin/C-peptide secretion results have been shown to have excellent correlations ($r > 0.85$, $P < 0.001$) with the number of islets transplanted intrahepatically in a cohort of TPIAT recipients with successful islet grafts.[50] Although not yet studied routinely before TPIAT, this parameter has the potential to predict the number of functioning islets patients have before pancreatectomy, and a parameter of the number of islets functioning after transplantation during years after transplantation.

α-Cell function is evaluated best by performing hypoglycemic, hyperinsulinemic clamps. This study establishes the glucose level at which glucagon secretion begins and hypoglycemic symptoms occur. Glucagon is the primary counter regulator of hypoglycemia by virtue of its stimulatory effect on hepatic glycogenolysis. Unfortunately, however, glucagon responses from islets transplanted intrahepatically are greatly suppressed, whereas their responses to intravenous arginine are less impaired,[51] indicating the defect in secreting glucagon is specific to hypoglycemia, and cannot be explained by reduced surviving islet mass. The mechanism for the glucose sensing defect may be increased glucose flux within the liver during glycogenolysis and hypoglycemia, which masks intrahepatic α cells to the stimulatory effects of low blood glucose in the general circulation.[52] Glucagon secretion induced by hypoglycemia was normalized and hypoglycemic awareness improved by transplantation of a portion of the islets into the peritoneal cavity in younger recipients of a larger number is autoislets, supporting a site-specific defect in α-cell function.[51]

In addition to impaired glucagon responsiveness, islet engraftment in the liver is also associated with a deficiency of pancreatic polypeptide (PP) release[53]; a loss of nutrient-stimulated PP secretion in CP contributes to hepatic insulin resistance. The combined deficiency of glucagon and PP responsiveness in transplanted islets recapitulates the defect seen in other versions of pancreatogenic or type 3c diabetes.

Although islet autotransplants differ from allografts in their lack of immunogenicity, the procedure of islet transplantation is very similar. Thus, knowledge gained through islet allotransplants for type 1 diabetes is relevant to the field of islet autotransplantation. The Edmonton protocol established that glucocorticoid-free immunosuppression utilizing low-dose calcineurin inhibitor (tacrolimus) in combination with an mTOR inhibitor (sirolimus) was compatible with rendering recipients insulin independent, but required the infusion of islets from more than 1 donor pancreas. Insulin-free status was often achieved but islet graft function subsequently declined. Even in insulin-independent islet recipients, the β-cell

secretory capacity was only approximately 25% of normal, evidencing a markedly reduced engrafted islet β-cell mass.[54] This reduced engrafted islet β-cell mass is just at the margin of what is required to avoid hyperglycemia, and so likely explains the eventual return to insulin therapy in the majority of recipients treated by the Edmonton protocol. Moreover, the lower functional islet β-cell mass for the numbers of islets transplanted suggested an early loss of islets that might be attributed to nonspecific inflammatory and thrombotic mechanisms.

The multicenter Clinical Islet Transplantation 07 protocol incorporated strategies to promote allogeneic islet engraftment based on T-cell depleting antibody (thymoglobulin) with TNF-α inhibition (etanercept), heparinization, and intensive insulin therapy (for 8 weeks) in the peritransplant period, together with the same low-dose tacrolimus and sirolimus maintenance immunosuppression as in the Edmonton protocol.[55] In the 11 subjects transplanted at the University of Pennsylvania, this combination of immunosuppressive, anti-inflammatory, antithrombotic, and β-cell "rest" approaches was associated with an improvement in β-cell secretory capacity to more than 40% of normal despite the transplantation of fewer islets than in the same institution's previous experience with the Edmonton protocol, with 7/11 Clinical Islet Transplantation 07 protocol subjects receiving islets from a single-donor pancreas, and suggesting a 3-fold gain in islet engraftment efficiency.[55] Importantly, when the Clinical Islet Transplantation 07 protocol cohort was reassessed at 1 year, they remained free of insulin use with a trend toward further improvement in β-cell secretory capacity to more than 50% of normal,[55] supporting the achievement of a sufficient engrafted β-cell mass capable of resisting metabolic exhaustion over time. Although islet autotransplants do not necessitate immunosuppression, use of adjuvant anti-inflammatory agents, heparinization, and aggressive insulin therapy are relevant to TPIAT.

Research Gaps and Opportunities

Preservation of islet β-cell mass and functionality is recognized as instrumental for the success of islet transplantation. Factors and mechanisms of β-cell destruction have been identified at various stages of the procedure and may be targeted therapeutically. Few agents have been studied under a randomized and controlled approach, which will be needed to clearly demonstrate efficacy in this complicated population. Overall, the aim is to improve β-cell number, enhance engraftment, and preserve long-term function. Although this may include small pilot studies, results should be validated in larger randomized trials, which may require a multicenter consortium.

In addition, as we try to understand more of the mechanisms involved in β-cell loss and their short- and long-term relationship with the host organ, new tools for β-cell monitoring should be developed. Specific research priorities in this area include the following:

- Clinical trials with therapeutic interventions early after islet transplantation directed at known detrimental factors. Potential approaches include antiapoptotic strategies, anti-inflammatory agents, antithrombotic approaches, prevascularized alternative sites, or pharmacotherapy to increase vascularization. Clinically available agents, many with promising preclinical or alloislet data to support their use, include TNF-

α and IL-1 inhibition, α-1 antitrypsin, and dextran sulfate; others are in preclinical development.

- Improving early glucose control through currently available and future diabetes technologies.
- Define mechanisms that underlay long-term islet graft survival, such as chronic islet stress, ER-stress pathways, and islet amyloidosis; these remain more uncertain and worthy of study.
- Develop new tools for β-cell monitoring, including functional testing or biomarkers. Define and study potential biomarkers for islet loss.
- Because islet functionality may be impaired when transplanted into the liver, more studies should focus on studying β-, α-, and PP-cell function before and after TPIAT to monitor survival of islets in the long term (>3 years after islet autotransplantation) and understand posttransplant changes.
- Careful assessment in controlled prospective trials of placement of a portion of the transplanted islets into nonhepatic sites to preserve α-cell function; questions remain as to the contribution of prepancreatectomy function, islet mass, glucose sensing, and hepatic extraction of islet hormones secreted from various sites for metabolism.

IMPROVING OUTCOMES AFTER TOTAL PANCREATECTOMY

Overview of the Problem

Pain, the cardinal feature of CP, has been difficult to treat effectively despite a multitude of empirical therapeutic approaches. A prospective cohort study of 540 patients in the North American Pancreatitis Study 2 found that 77% of patients self-reported a defined pain pattern. These patients had a significant burden of disease as represented by QoL metrics (12-Item Short-Form Health Survey) and more than 25% were on disability benefits.[56] Recent studies, both human and experimental, have indicated a critical role for neuronal mechanisms resulting in peripheral and central sensitization, pointing to novel therapeutic targets. The pancreatic nociceptor seems to be significantly affected in this condition with increased excitability, associated with downregulation of potassium currents. Some of the specific molecules implicated in this process include the vanilloid receptor, transient receptor potential cation channel, subfamily V, member 1, nerve growth factor, the protease activated receptor 2, and a variety of others. This suggests that future research may identify improved methods for pain management in CP.[9,57]

Despite the observation that GI dysmotility is a problem in CP and after TPIAT, systematic studies are lacking.[58–62] Data on gastric motility after non-TPIAT pancreatic surgery demonstrate delayed gastric emptying in 45% to 50% of patients with CP, and in 14% to 20% of patients after pancreatectomy.[59–63] An internal review at Johns Hopkins showed that 40% of patients experienced delayed gastric emptying after TPIAT. Nausea, vomiting, poor oral intake, and constipation are common problems in both patients with CP and those after TPIAT.

The pancreas plays an essential role in the digestion and absorption of nutrients.[63,64] CP may lead to malnutrition by multiple mechanisms, including malabsorption, decreased intake for fear of exacerbating pain, dietary restrictions, nausea, or gastric emptying problems. CP may lead to EPI. TPIAT is always followed by a lifelong need for PERT. Current assessment tools for EPI, including 72-hour fecal fat, CCK/secretin–stimulated pancreatic function testing, and fecal elastase each have limitations, leading to underdiagnosis of EPI in CP. Dosing of pancreatic enzymes in patients with exocrine insufficiency is highly variable, and many patients are undertreated. Monitoring of nutrition in CP or after TPIAT (fat soluble vitamins, vitamin B12, weight, muscle mass, and bone health) is performed sporadically, depending on the individual center.[13,64]

As with adults, CP in children is progressive, often starting with recurrent episodes of acute pancreatitis. Fifty to seventy percent of children with CP have genetic mutations that predispose them to the condition. Consequently, limited resections of the pancreas or therapies aimed at improving drainage rarely provide lasting relief from intractable pain and frequent hospitalizations that limit school attendance and reduce QoL. Initial management is medical and endoscopic, but if those fail these children should be considered for TPIAT because children tolerate the operation well and have durable improvement in pain.[65]

QoL improves in physical and mental components for children after TPIAT. School attendance and activity levels return to normal for essentially all patients. Insulin independence is higher for younger children than for teenagers and adults, and seems durable with limited follow-up.[66] Among 75 children who received TPIAT for CP unresponsive to medical, endoscopic, or surgical treatment, pain and the severity of pain statistically improved in 90% of patients after TPIAT, with sustained relief from narcotic use. More than 40% achieved insulin independence. By multivariate analysis, 3 factors were associated with insulin independence after TPIAT: (1) male sex, (2) lower body surface area (correlates with younger age), and (3) higher islet mass transplanted. Total IEQ was the single factor most strongly associated with insulin independence (OR 2.62 per 100,000 IEQ). TPIAT is an effective therapy for children=with painful pancreatitis that fail medical and/or endoscopic management.[13,66]

Research Gaps and Opportunities

There is limited understanding of the pathophysiology of pain and GI motility in CP, and limited strategies for management of both. Development of pain management strategies for patients before surgery is crucial, but must be done in conjunction with assays for pancreatic function to insure that control of pain does not mask organ deterioration. Identification and management of dysmotility and narcotic bowel syndrome is important. Optimal monitoring and management of EPI in CP is as yet undefined; it will be important to establish a comprehensive nutritional assessment and metrics for quantifying EPI to measure the effect of CP and TPIAT on nutritional status. A better understanding of the pathophysiology and natural history of CP in children and the extent and type of medical and endoscopic interventions that should precede TPIAT in children is needed.

Specific research priorities in this area include the following:

- Develop comprehensive CP and TPIAT registries that can be used for prediction modeling and better outcomes determinations.
- Development of standard measures before and after surgery, including nutritional, psychiatric, and pain testing.
- Developing a better understanding of the pathophysiology of painful CP, including the roles of central versus peripheral pain sensitization, and the influence of genetic factors on the rate of progression and severity of pain.[9,57]
- Measurement of pain severity, including biomarkers for painful versus nonpainful CP; assessment of neuropathic pain or sensitization; and strategies for overcoming the limitation of visceral sensory convergence that complicates distinguishing pancreas-specific pain from other sources of pain.
- Trials assessing the utility of nonnarcotic pain and nausea management tools, including exercise, stretching, visual imaging, hypnosis, cognitive behavioral therapy, and other nontraditional therapies.
- Trials of optimal postoperative pain management and weaning protocols; these should include measurable endpoints such as returned to work/school, narcotic independence, or pain-free status.
- Better understanding of the impact and treatment of emotional and psychological changes before and after TPIAT.
- Improved approaches to assess and treat dysmotility and narcotic bowel syndrome after TPIAT.
- Characterization of GI tract motility in CP before and after TPIAT, including delayed or rapid gastric emptying, small intestinal and colonic motility. The usefulness of currently available tests for dysmotility (4-hour gastric emptying study, wireless motility capsule, whole-gut scintigraphy, and Sitzmark testing) has not been examined in CP or TPIAT and should be assessed.
- Studies of promotility agents before and after TPIAT.
- Interaction between motility and other GI complications in TPIAT such as small bowel bacterial overgrowth, constipation, and diarrhea.
- Role of the vagal nerve, GI/pancreatic hormones, and tissue markers may be useful in determining the pathophysiology of dysmotility and developing improved testing and therapy.
- Optimal management of EPI, including evidenced-based recommendations on the dosage, timing of dose, and type of PERT (coated, uncoated, mixed), and how additional therapies (for example, proton pump inhibitors) might improve absorption.
- Determine factors that contribute to failure of PERT after TPIAT.

- Assessment of the impact of malabsorption (of nutrients, fat soluble vitamins, vitamin B_{12}, calcium, magnesium, zinc, and folic acid) on other factors in digestion and absorption including salivary amylase, gastric lipase, and bile acids.
- Development of better tests for EPI, including ones that might monitor adequacy of PERT dosing, is needed.
- Assessment of sarcopenia as an early indicator of failure of medical management of CP and as a prognostic factor for outcome after TPIAT.
- Definition of the impact of obesity on intrahepatic transplanted islets, including whether non-alcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) impact islet function, or whether islets impact liver function in this setting.
- Characterization of the pH of the intestine in patients who underwent TPIAT with and without cystic fibrosis transmembrane conductance regulator (CFTR) mutations (and an assessment of implications for solubility of bile acids and enzymes).
- For children with CP, a better understanding of the natural history of CP is needed, with long-term goal to identify treatments that interrupt the progression from disease onset to irreversible changes in the pancreas and persistent symptoms.
- Development of methods to identify children whose CP will progress quickly, to identify the optimal time to rescue islets.
- Identify factors that prolong transplanted islet function in young children particularly, or which could promote islet growth and expansion.

REGULATION OF ISLET TRANSPLANTATION BY THE FOOD AND DRUG ADMINISTRATION

The FDA has published guidelines for the regulation of human cells and tissues, including islet transplantation (21 CFR 1271). These regulations are commonly referred to as the tissue rules and are focused on preventing the spread of communicable diseases. The tissue rules include provisions for registration of facilities, determination of donor eligibility, and compliance with Current Good Tissue Practice. In some cases, human cells and tissues are also regulated as biological drugs and are subject to additional regulations relevant to biologics and drugs. Autotransplantation of islets is only subject to the tissue rules and centers performing autotransplantation should be registered with the FDA and should follow Current Good Tissue Practices. Allotransplantation of islets is subject to both the tissue rules and the biologic and drug provisions. Allotransplantation should be studied under an investigational new drug application submitted to the FDA.

REGISTRY CONSIDERATIONS FOR TPIAT

Overview of the Problem

Robust and long-term cooperative research consortia or registries between academic centers are needed to pool collected data from TPIAT recipients for adequate interpretation of results and to power further studies. The Collaborative Islet Transplantation Registry (CITR)

has collected information during the last 15 years, however mostly from patients who have received allogeneic islet transplantation. Further, the endpoints in CITR are focused only on diabetes aspects of the procedure. Thus, it is important to develop registries for patients with CP who are candidates for TPIAT with emphasis on preoperative evaluation and postoperative clinical outcomes of relevance to this group such as pain, narcotic use, GI function–dysfunction and dysmotility, nutritional status, need of exocrine replacement therapy and integral QoL measures. In addition, it is essential to have assessments of islet function, insulin independence and glucose control measurements similar to those used for allogeneic islet transplantation. For this, it is important to create standardized questionnaires and measures of appropriate outcome metrics.

The CITR registry is a voluntary collection of data from participating centers performing allo- (n 902 recipients) and autoislet transplants (n = 587 recipients), but=follow-up data for autotransplants are far less complete than for allotransplants. Primary outcomes are reported at annual time points for allogeneic islet recipients and for TPIAT. Recipient, donor, procurement and processing characteristics, are collected to identify the most favorable factors predicting good clinical outcomes. The primary outcomes, all specific to diabetes, are described as prevalence at each annual time point of: insulin independence (defined as no exogenous insulin >14 days); fasting C-peptide 0.3 ng/mL or more (an indicator of islet function), fasting blood glucose less than 140 mg/dL, and number of severe hypoglycemia episodes.

The most relevant differences seen between islet allotransplantation and autotransplantation in the CITR include considerably fewer IEQs infused in TPIAT (median, 255 K) than for allotransplants (median, 400 K) and less use of islet culture periods in TPIAT. Cold storage time for autotransplants has declined substantially during the era of the registry. Despite the lower total IEQs typically administered, TPIAT exhibits success rates that are very comparable to allotransplants especially in restoration of euglycemia and avoidance of severe hypoglycemic events. Outcomes in patients with pancreatectomy but no islet autotransplant would be useful to collect for comparison purposes.

Because TPIAT is an extensive and irreversible surgical procedure, it is crucial to have a detailed assessment of the patients before surgery. Etiology of disease should be defined. The toxic–metabolic, idiopathic, genetic, autoimmune, recurrent or severe acute, and obstructive disease classification[67] is often used and covers the potential causes including toxic–metabolic, idiopathic, genetic, autoimmune, recurrent or severe acute, and obstructive disease. History of smoking (an important toxic risk factor) should be assessed. Rationale for intervention should be defined, which may include intractable pain, impending pancreatogenic diabetes, fear/risk of pancreatic cancer or poor QoL. Consensus recommendations from *Pancreas Fest* 2012 include that presurgical evaluation should confirm the diagnosis of diabetes, and assess for presence of diabetes, β-cell mass, liver health, and patency of the portal vein.[65,68] The trajectory of disease should be described, along with patient disability, patient age, pain pattern, and narcotic requirements. Repeated measures should be made over time to determine disease progression and potential interventions to prevent the need for TPIAT. There is also great value in the analysis of tissue samples, when available, to catalyze research for the elucidation of mechanisms and

the identification of biomarkers (eg, molecular, imaging, hormonal) to better characterize the response to TPIAT.

Reports by several international centers have demonstrated the safety record and efficacy of TPIAT to alleviate symptoms and complications of refractory CP and prevent diabetes mellitus.[69,70] An obstacle for the further application of TPIAT is the lack of organized multicenter studies that illustrate these benefits, and a multicenter, international, comprehensive post-TPIAT data collection would contribute to broader application of TPIAT globally. There is need for inclusion of multidisciplinary data elements that go beyond diabetic assessments in the CITR, such as pain management, narcotic use, GI symptoms, operative complications, QoL and resource utilization/financial performance. The registry can also be expanded to include patients undergoing TPIAT after treatment of pancreatic malignancies.[71]

Research Gaps and Opportunities

There is uniform agreement that a multicenter registry in TPIAT is critical to advancing the field. This should address pain, GI, and diabetes outcomes. Specific research gaps exist in our ability to define pathologic mechanisms that lead to unmanageable CP and the need for TPIAT. Benefits of TPIAT need to be compared to other standard surgical procedures for CP. A registry mechanisms should include standardized data collection for clinical/laboratory data, manufacturing processes, surgical approaches, and pre- and postprocedure care.

Specific research priorities include the following:

- Multicenter collaboration with a data collection registry and biorepository for essential pre- and postoperative measures, tissue and fluid samples, and outcomes with mechanisms for long-term follow-up of all patients undergoing TPIAT. Whether within the existing CITR or an independent registry, support for ongoing data entry is critical.
- Further research on the pathophysiology of CP and the potential development of interventions that may alleviate pain and other symptoms without the need for surgery.
- Exploration of novel diabetes technologies before and after TPIAT.
- Further research on mechanisms of CP complications and the identification/validation of biomarkers of CP.
- Well-designed advanced clinical trials to validate the benefit of TPIAT.
- Development of predictive and efficacy/outcome models for TPIAT.
- Discussion of new methods of data management adapted to TPIAT.

CONCLUSIONS

Numerous themes and needs emerged from the workshop, particularly the need for standardization of care (before surgery, during surgery, and after surgery) and creation of

guidelines together with a comprehensive registry to allow analysis of large number of patients to determine which patients are appropriate candidates for TPIAT and help direct care. A multidisciplinary approach is essential and the importance of addressing other psychological comorbidities was stressed in multiple sessions.

Currently, more than 15 academic institutions through the United States have active TPIAT programs and the number is rapidly growing. Debilitating pain from CP is the major indication for TPIAT. Thus, developing simple and accurate criteria for the early diagnosis of noncalcific normal size pancreatic duct CP, and distinguishing CP pain from other painful abdominal conditions are urgently needed. Controlled clinical studies are necessary to determine timing of surgery related to onset of symptoms, best surgical therapy (TPIAT vs other decompressive surgical procedures), and the role of ERCP. Pain measures should be developed to differentiate visceral pain from central sensitization. To reduce the risk of diabetes after surgery, research should focus on advancing islet isolation, islet engraftment, and assessment of functional (engrafted) islet cell mass. Alternative sites should be studied carefully for potential benefit in reducing IBMIR and improving function of α cells (glucagon secretion to hypoglycemia). Nutritional status before and after TPIAT, approach to PERT, GI dysmotility, and optimal pain management remain under-studied areas in TPIAT. A simple multicenter registry approach could help address many questions in the field.

This multidisciplinary symposium provided the stage for the exchange of information and ideas among different institutions offering the same surgical intervention, using different protocols and facing similar problems. We all agree that guidelines/standardization of care and further research studies are needed to advance the use of TPIAT in adults and children with CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the contributions of the invited speakers at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop on TPIAT, whose presentations comprise the content which is summarized herein: Dr David Adams, Dr Balamurugan Appakalai, Ms Franca Barton, Dr Gregory Beilman, Dr Melena Bellin, Dr Srinath Chinnakotla, Dr Ashley Dennison, Dr Martin Freeman, Dr Andres Gelrud, Dr Marlon Levy, Dr Mark Lowe, Dr Katherine Morgan, Dr Pankaj Pasricha, Dr Andrew Posselt, Dr Michael Rickels, Dr Paul Robertson, Dr Sara Jane Schwarzenberg, Dr Vikesh Singh, Dr Ellen Stein, Dr David Witcomb, and Dr Keith Wonnacott. A full listing of the National Institute of Diabetes and Digestive and Kidney Diseases TPIAT Workshop Faculty and Organizing Committee may be found in a supplement (Supplemental Digital Content available at http://links.lww.com/MPA/A332) to this article in the online version of *Pancreas*.

The authors also thank the Office of Rare Disease Research, National Center for Advancing Translational Sciences, NIH, and the National Pancreas Foundation for additional support. The authors are grateful for the on-site support of Ms Patter Birsic, Ms April Burford, and Mr Matthew Alsante of the National Pancreas Foundation, and Ms Joy Merusi of the Department of Medicine, University of Pittsburgh Medical Center.

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TABLE 1

Example of 1 Proposed Patient Selection Protocol for TPIAT[69]

Patient must fulfill criteria 1–5 given in the following text.
1. Diagnosis of chronic pancreatitis, based on chronic abdominal pain of >6-mo duration with at least 1 of the following:
Pancreatic calcifications on CT scan.
At least 2 of the following: ≥4/9 criteria on EUS, compatible ductal or parenchymal abnormalities on secretin MCRP; abnormal endoscopic pancreatic function tests (peak Hco_2 ≤80 mM).
Histopathology confirmed diagnosis of chronic pancreatitis.
Compatible clinical history and documented hereditary pancreatitis (*PRSS1* gene mutation).
Or
History of recurrent acute pancreatitis (more than 1 episodes of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase >3 times upper limit of normal).
2. At least 1 of the following:
Daily narcotic dependence.
Pain resulting in impaired quality of life, which may include: inability to attend school, recurrent hospitalizations, or inability to participate in usual, age-appropriate activities.
3. Complete evaluation with no reversible cause of pancreatitis present or untreated.
4. Failure to respond to maximal medical and endoscopic therapy.
5. Adequate islet cell function (nondiabetic or C-peptide positive)
Patients with C-peptide negative diabetes meeting criteria 1–4 are candidates for TP alone.

CT indicates computed tomography; EUS, endoscopic ultrasound; MRCP, Magnetic Resonance Cholangiopancreatography.