Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis Relieves Pain and Mitigates Diabetes Development

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ABSTRACT

Introduction: By removing the intrinsic source of pain, total pancreatectomy offers patients with chronic pancreatitis a definitive surgical treatment. However, pancreatectomy results in labile diabetes. Specialized centers perform total pancreatectomy and islet autotransplantation (TP-IAT) to prevent labile diabetes and restore insulin independence after pancreatectomy.

Objective: The objective of this retrospective study was to describe current indications and outcomes of TP-IAT performed at the University of Wisconsin (UW)–Madison, the sole center in the state offering this procedure.

Methods: We reviewed the records of 19 TP-IAT procedures performed at our center from 2014 to 2023 for chronic and relapsing pancreatitis. All were nondiabetic and 89% required narcotics for pain. We report surgical outcomes as well as outcomes related to postoperative control of pain and diabetes, including narcotic usage, islet graft function (measured by detectable fasting serum C-peptide levels), and insulin independence.

Results: The UW experience with TP-IAT demonstrates durable pain alleviation in 79% of patients. One year post-procedure, 80% of patients exhibited islet graft function; 32% remained insulin-independent.

Conclusions: In selected nondiabetic patients with chronic pancreatitis, TP-IAT is associated with durable reductions in narcotic pain medication requirements, improved quality of life measures, islet function, and mitigation of insulin dependence. Despite the advantages of TP-IAT, the procedure is still underutilized in the United States. Our data indicate that nondiabetic patients with chronic pain syndromes due to pancreatitis should be referred for possible TP-IAT to specialized centers before they lose islet function, develop significant fibrosis/calcifications, or have other major pancreatic surgical procedures.

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INTRODUCTION

Total pancreatectomy and islet autotransplantation (TP-IAT) is an established surgical procedure that alleviates incapacitating pain and improves the quality of life (QoL) for patients with chronic pancreatitis (CP). The primary aim of TP-IAT is to relieve pain and suffering from either CP or recurrent acute pancreatitis (RAP). The secondary goal is to prevent brittle diabetes through islet autotransplantation. Since TP-IAT was first performed in 1977 at the University of Minnesota, procedures have expanded to several centers across the United States and in Europe. However, the islet isolation portion of the procedure can be performed only at specialized centers, such as the University of Wisconsin (UW)-Madison's UW Health Transplant Center.

A TP-IAT procedure generally is offered to CP/RAP patients who have persistent or progressive symptoms despite optimal medical management or where endoscopic procedures have failed to relieve pain sufficiently. After the pancreas is removed from the patient, the gland is taken to a facility certified to perform pancreas digestion and islet isolation. Following operative reconstruction of the biliary drainage and intestinal continuity, the islets are returned to the operating room for infusion directly into the patient's portal vein.

Compared to pancreatectomy alone, TP-IAT increases patient quality-adjusted life years and improves blood glucose control. TP-IAT is a cost-effective treatment for chronic pancreatitis, with perioperative costs offset by savings from decreased hospi-

talizations, endoscopy, and imaging.[1] Outcomes data from several recent excellent reviews,[2-4] reports of consensus conferences,[5-8] and large single-center studies[9-18] have been published. Experiences indicate a low perioperative mortality of 1.2% to 2.1%,[8] and a 1-year patient survival rate of 95%.[19] The overall 30-day morbidity and complication rates are approximately 30% to 60%, similar to that of other complex pancreatic surgeries.[8,20]

Herein, we report the surgical, pain relief, and diabetes control outcomes of TP-IAT over the last 10 years of our experience at the UW Health Transplant Center.

METHODS

Patient Population and Analytic Approach

UW began performing TP-IATs in 2005. Islet cell isolation data prior to 2014 was not available. Therefore, patients who underwent TP-IAT from 2014 to 2023 were included in our sample.

We reviewed the medical records and islet cell isolation data of the patients who underwent TP-IAT at UW. Data were abstracted from provider notes, laboratory results, and imaging between referral for TP-IAT and last follow-up (if continued islet function) or graft loss. Variables included patient demographics, medical history focusing on pancreatitis symptoms and prior attempted interventions (endoscopy, regional blocks, surgery), operative complications, narcotic usage before and after surgery, and perioperative and postoperative islet function. We documented outcomes for up to 1 year post-transplant. Islet cell isolation data collection focused on explanted pancreas quality and weight and islet cell yield and purity.

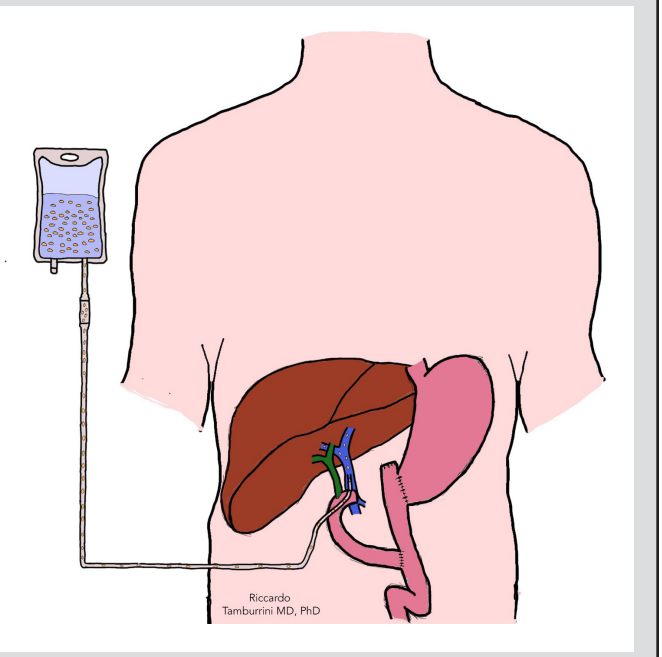
Preoperative Patient Management

Islet function is assessed using fasting C-peptide, a 2-hour oral glucose tolerance test, and hemoglobin A1c. At least 4 weeks in advance of the TP-IAT surgery, in preparation for splenectomy, all patients are screened and vaccinated (as necessary) for *Haemophilus influenzae* type B, pneumococcus (PCV13, PCV 20 or 23), and meningococcus (meningococcal ACWY and B). On the day of surgery, the regional anesthesia team performs an epidural in the preoperative area. Patients receive preoperative antibiotics, typically ampicillin and ceftriaxone.

Surgical Procedure

Pancreatectomy: After informed consent, a total pancreatectomy, splenectomy, and cholecystectomy are performed using techniques to minimize pancreas warm ischemia to preserve the islets of Langerhans. All patients receive perioperative anticoagulant therapy (heparin, 5000 units subcutaneous). The spleen and body and tail of the pancreas are mobilized and resected first, followed by resection of the head of the pancreas en-bloc with the duodenum. Upon removal from the operative field, each portion of the pancreas is placed on ice and flushed with cold UW solution. The surrounding tissues, including the duodenum, are removed, and the pancreatic duct is cannulated in each portion of the pancreas.

Figure 1. Anatomic Reconstruction With Infusion of Islet Cells Into the Portal Vein During Total Pancreatectomy and Islet Autotransplantation



Islet Isolation: The pancreas pieces are packaged sterilely and transported in cold UW solution to UW's Good Manufacturing Practice isolation facility. The islets are isolated using a modified automated Ricordi method. The parenchyma is broken apart by a combination of enzymatic and mechanical digestion in a Ricordi chamber.[21] Next, the islets are resuspended in cold solution to quench the digestion process. After washing, a measured sample of islets is stained and examined microscopically to quantify the yield of the isolation process as an islet particle and islet equivalent number. If required, further islet purification is performed. After calculation of the final islet yield, the islets are washed again and suspended in 5% human albumin and heparin at 70 units per kilogram of recipient body weight. Samples are collected from the pancreas recovery/transport solution and the final islet suspension for Gram stain and bacterial/fungal culture. Results are reported directly to the patient's clinical team.

Gastrointestinal Reconstruction: While the islet isolation procedure is underway, the surgical team performs a gastrointestinal reconstruction (Figure 1). To restore biliary and gastric drainage, a retrocolic choledochojejunostomy and retrocolic gastrojejunostomy are fashioned in a Roux-en-Y configuration. A gastrojejunal feeding tube is placed for gastric decompression and postpyloric enteral feeding.

Islet Infusion: Thirty minutes before the islet autotransplant, an intravenous (IV) infusion of etanercept is started. Etanercept, a

tumor necrosis factor receptor inhibitor, is used to decrease the instant blood-mediated inflammatory response that can contribute to islet cell destruction. Islets are then infused into the liver via direct cannulation of the main portal vein. Portal venous pressure is monitored before, during, and after infusion; the infusion is stopped if the pressure is sustained above 25 cm H_2O (18 mmHg). If additional islets remain at this point, they can be implanted in an alternative site, such as the peritoneal cavity. After islet infusion, the incision is closed.

Postoperative Recovery and Patient Care

The entire surgery typically lasts 7 to 8 hours. After surgery, patients are moved to the transplant floor. If there are no complications, patients remain inpatient for approximately 2 weeks. Given the variable preoperative usage of narcotics for chronic pain, the acute pain service is consulted to assist with the management of patients' postoperative pain. A multimodal pain regimen typically includes the previously described epidural and a patient-controlled analgesia pump for narcotic administration; scheduled acetaminophen, ketorolac, and ketamine are employed occasionally as adjunctive therapies.

In the immediate postoperative period, insulin is given by IV infusion to maintain glycemic control and avoid stressing the islet cells in order to optimize islet engraftment. This is typically transitioned to subcutaneous administration within 3 to 4 days. The majority of patients undergoing TP-IAT are discharged from the hospital with temporary insulin dosing to control blood glucoses. Gradually, insulin is weaned postoperatively over the first several months.

Patients receive continuous IV antibiotic coverage for 48 hours. Once bowel function resumes, patients' diets are advanced and pancrelipase is initiated for pancreatic exocrine enzyme replacement. Additional doses of etanercept are administered on postoperative days 3, 6, and 10. All patients receive postoperative anticoagulant therapy (prophylactically dosed subcutaneous low molecular weight heparin) for 4 weeks postoperatively.

Data Analysis

We calculated standard descriptive characteristics for our aggregate sample. Preoperative and postoperative data were rendered graphically using GraphPad Prism version 10.4.2 for Macintosh (Boston, Massachusetts).

RESULTS

Patient Characteristics

During 2014 through 2024, 20 patients were scheduled for TP-IAT at our instititution. One attempted islet cell isolation was not successful due to extensive replacement of the pancreatic parenchyma with scarring from chronic pancreatitis. The remaining 19 patients are included in our analysis.

The patients were 63% female, 95% were White, and the mean age was 39 years (range 16-74 years) at the time of surgery. The mean age at first diagnosis of pancreatitis was 32 (range 6 months-69 years). The etiologies of pancreatitis included anatomic (32%, most commonly pancreas divisum), genetic conditions (26%), idiopathic (21%), surgical or traumatic injury (10%), and alcohol and hypertriglyceridemia (10%).

At the time of referral for TP-IAT, most patients had been having pancreatitis symptoms for 7 years. The majority (89%) utilized narcotics for pain control; the 17 patients who used opioids reported taking a median of 48 milligrams of morphine equivalents per day (mean 97 morphine equivalents, range 15-296). Gastrointestinal symptoms were common, with 74% experiencing nausea and/or vomiting regularly, 74% reporting weight loss, and 32% noting bloating. Twenty-one percent received tube feeds, and 16% required total parenteral nutrition at some point during the 5 years prior to TP-IAT. Sixty-eight percent of patients were receiving pancreatic exocrine enzyme supplementation prior to surgery.

The number of patient-reported pancreatitis flares in the year prior to TP-IAT ranged from 1 to 30, with most patients noting 3 to 12 episodes. Health care utilization was high. One patient presented to the emergency department (ED) 24 times within the 5 years prior to TP-IAT. Another had 15 inpatient admissions and an additional 22 ED visits in the 3 years prior to TP-IAT. Per provider notes, some patients reported limiting their ED visits and attempting to manage their pancreatitis episodes at home. The majority had at least 1 endoscopic retrograde cholangiopancreatography (ERCP) (74%), often with stent placement or sphincterotomy. Half (47%) had a celiac block. Two-thirds (68%) had undergone abdominal surgery; cholecystectomy was the most common procedure (53%). Only 1 patient (5%) had a prior pancreatic surgery.

Seven patients (37%) had morphologic changes to the pancreas on endoscopic ultrasound, 1 (5%) had pancreatic calcifications on cross-sectional imaging, and 2 (10%) had both morphologic changes and calcifications. Prior to TP-IAT, none of the patients in our sample required insulin. The mean C-peptide was 1.5 ng mL (range 0.6-3).

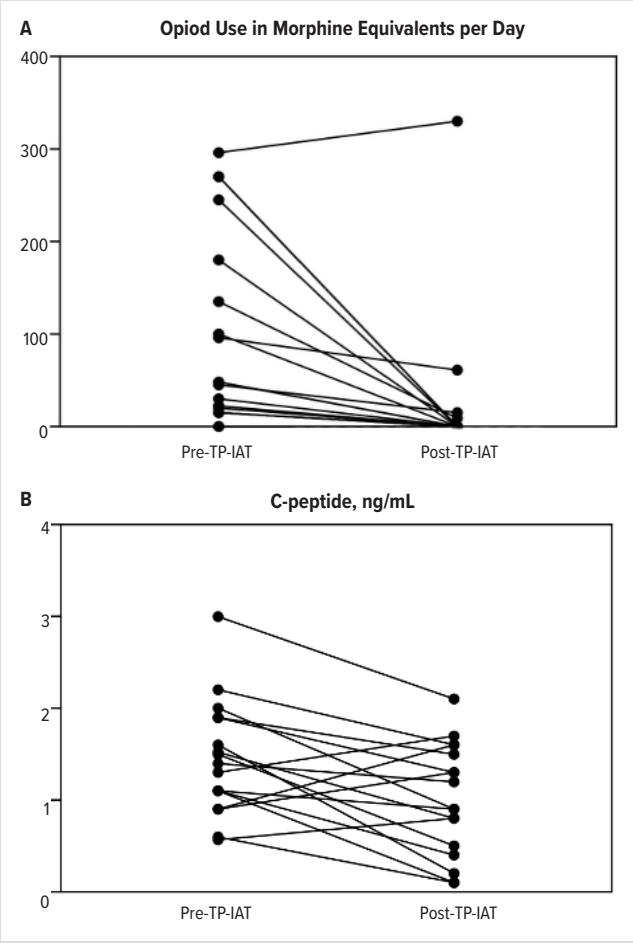
Islet Isolation

The mean post-trimming pancreatic explant weight was 114 grams (range 64-180 grams). Many pancreata had stigmata of chronic inflammatory changes, with 58% having severe or moderate fibrosis and 37% having moderate or severe calcifications. The mean total islet yield was 206 367 islet equivalents (IEQs) (range 19 090–687 000 IEQs), which provided a mean of 2946 IEQs per kilogram of body mass (range 300-8696 IEQ/kg).

Patient Outcomes

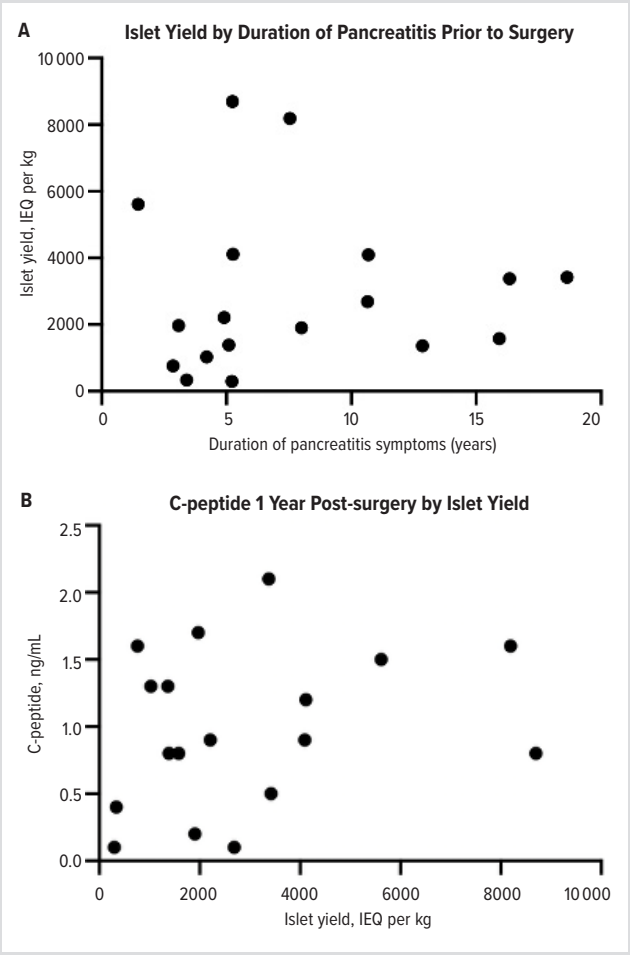
All patients were alive 1 year post-TP-IAT. Two patients (11%) were admitted to the intensive care unit postoperatively. One

Figure 2. Outcomes for the University of Wisconsin TP-IAT Patients, Before and After TP-IAT



Abbreviations: TP-IAT, total pancreatectomy and islet autotransplantation.

Figure 3. Outcomes for the University of Wisconsin TP-IAT Patients



Abbreviations: TP-IAT, total pancreatectomy and islet autotransplantation; IEQ, islet equivalents.

patient (5%) had a colonic injury and required reoperative wound management. During the index admission, 1 patient (5%) developed a sterile intraabdominal fluid collection that was drained by interventional radiology. Five patients (26%) had a postoperative ileus necessitating the replacement of a nasogastric tube. The mean time to discharge was 16 days (range 8-35 days).

The 30-day readmission rate was 32%. Reasons for admission included abdominal pain (10%), failure to thrive (10%), clostridium difficile and feeding tube dislodgement (5%), and transient gastric outlet obstruction that resolved with nonoperative management (5%). Between 2 and 12 months postoperatively, one-quarter of patients (26%) had another surgery: 4 patients required lysis of adhesions, and 1 patient underwent gastrojejunostomy revision. Reoperation within 1 year was more common in the earlier period prior to 2016.

One year after TP-IAT, 79% of patients had durable pain relief. Only 4 patients were still taking narcotics. One patient's daily total had increased from 296 to 330 morphine equivalents. The other 3 patients who were still using opioids had decreased their doses by 50% to 90%. Thirteen patients who had previously required narcotics no longer required pain medication. Figure 2A displays the narcotic requirements for each patient in our cohort before and after TP-IAT.

At 1 year post-TP-IAT, 32% of our cohort was insulin-independent. For the patients who required insulin, the average dose was 13 units per day (range 3-22 units). The mean postoperative C-peptide was 0.99 ng/mL (range <0.1-2.1 ng/mL). Among the 17 patients who had preoperative and postoperative data, 4 patients (21% of the cohort) had increased C-peptide levels post-TP-IAT and the other 13 patients (68% of the cohort) had decreased C-peptide levels (Figure 2B). Twelve of 15 patients (80%) had measurable post-transplant C-peptide (≥ 0.3 ng/ml) 1 year post-procedure indicating functional islets in the liver. The mean HbA1c prior to TP-IAT was 5.3% (range 4.7%-6.3%) and the mean HbA1c post-procedure was 7.3% (range 5.5%-9.4%). Figure 3A displays the islet equivalent yield per kilogram of patient weight by the duration of pancreatitis symptoms prior to surgery. Figure 3B examines the relationship between islet yield

and C-peptide levels 1 year post-surgery. These findings demonstrate that even patients who receive <2500 IEQ/kg of islets can achieve a degree of beta-cell engraftment and insulin production 1 year post-TP-IAT.

DISCUSSION

TP-IAT typically is utilized in patients with painful and debilitating chronic pancreatitis that has not responded to medical, endoscopic, and/or surgical therapies. Impairment in quality of life (QoL) due to pain should be substantial enough to justify the risks of major abdominal surgery, insulin-dependent diabetes, and pancreatic enzyme replacement therapy.[6,7] Thus, the subset of patients undergoing TP-IAT represents a subset of those undergoing total pancreatectomy (TP) and those with CP/RAP. Most centers, including UW, perform both TP alone and TP-IAT. Thus, patients referred to TP-IAT centers will undergo a comprehensive multidisciplinary evaluation to determine eligibility for either TP or TP-IAT. Generally, patients who are currently not taking insulin and have a HbA1c <6.5% are eligible for the IAT portion.

TP-IAT is a highly successful procedure when practiced in experienced centers with technically proficient teams. The patient survival and surgical complication rates at our insititution are consistent with, or better than, those of other major centers and reports. Patient survival in our series was 100% at 1 year compared to 95% 1-year survival rates reported by other large centers.[19] Due to the complexity of the surgery, readmission and reoperation rates are not trivial (UW 30-day readmission 32%; 1-year reoperation 26%). In comparison, published studies report overall 30-day morbidity of 36%,[20] and perioperative complication rates of 30% to 61%, which are similar to those of other complex pancreatic surgeries.[8]

Pain Control

Nearly every study of TP-IAT demonstrates resolution or significant reduction of pain and narcotic use in the majority of patients.[2,19,22] Complete relief or reduction of pancreatic pain is reported in up to 93% of adults and in 94% of pediatric patients at 1 year post-TP-IAT.[8] Opioid independence rates are reported to be 23% to 70% at 1 year and 73% to 84% at 5 years postoperatively.[8] At our center, we achieved opioid independence at 1 year in 79% of patients, matching or surpassing prior published results.

Nonetheless, the identification of factors associated with poorer pain relief outcomes is important for patient selection and preoperative counseling. Factors associated with less narcotic use and improved pain control outcomes include no previous pancreatojejunostomy or other pancreatic surgery, RAP patients, transient pain relief from celiac plexus blocks, young children, and genetic forms of pancreatitis (Table).[2,22] On the other hand, more than 3 prior stent procedures, long duration CP disease, obesity, and pancreas divisum are associated with less substantial pain relief in multivariate models.[2,22]

Table. Factors Associated With Opioid Independence and Insulin Independence Post-TP-IAT

Factors associated with opioid independence	Factors associated with insulin independence
• Genetic etiology for pancreatitis	• Non-alcoholic etiology for pancreatitis
• Recurrent acute pancreatitis	• Younger age
• Younger age	• Absence of diabetes before surgery
• Body mass index <30 kg/m^2	• No pancreatic calcifications or atrophy on imaging
• Fewer ERCP and pancreatic duct stents	• Shorter duration of pancreatitis
• No history of pancreatic surgery	• No prior pancreatic surgery
• Pain relief with celiac plexus block	• Islet mass at isolation >2500 IEQ/kg
• Lower preoperative opioid usage	

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

While TP-IAT may relieve pancreatic pain, new pain sources can arise. Some potential sources of new pain syndromes include gastroparesis, marginal ulcer, adhesions causing gastric outlet/small bowel obstruction, and central nerve sensitization.[2] The management of pain before and after transplant is best accomplished with multimodality approaches by a multidisciplinary team.

Diabetes Outcomes

Compared to TP alone, TP-IAT is associated with higher insulin independence rates and lower insulin requirements.[19] Insulin independence is associated with higher QoL scores, even when adjusted for other confounders.[23]

Infusion of islets into the liver typically results in insulin independence rates of 25% to 40% at 2 years post-procedure, with many centers reporting >20% insulin independence rates at 5 years.[3,19,23-25] Although some patients undergoing TP-IAT will never gain insulin independence and some will lose insulin independence slowly, approximately two-thirds of patients retain partial islet graft function long-term, defined by detectable fasting serum C-peptide levels.[26] In our series at 1-year post-procedure, we observed that 32% of patients were insulin-independent and 95% of patients demonstrated partial islet graft function, comparable to previously published reports. Retention of islet graft function helps prevent severe hypoglycemic events and stabilizes hyperglycemia, frequently resulting in HbA1c levels <7.0%, within the American Diabetes Association recommended targets. In contrast, after TP alone, patients necessarily develop "brittle" (labile and difficult-to-control) diabetes due to the complete absence of insulin, glucagon, and exocrine enzymes.

Preservation of functional pancreatic tissue predicts insulin independence post-TPIAT (Table), as higher islet yields are expected to achieve better glycemic control post-procedure. Shorter duration of CP, greater pancreatic tissue volume on preoperative imaging, the absence of prior major pancreatic extirpative or drainage surgery, and a lower preoperative HbA1c are consistently associated with better islet yields.[27,28] Early positive metabolic measures at 3 months, including islet dose and BETA-2 score, are associated with more favorable 1-year insulin independence rates.[29]

On the other hand, patients with adverse metabolic measures before surgery (HbA1c or elevated fasting glucose consistent with prediabetes) or lower islet yield (IEQ/kg <2500) experience worse glycemic outcomes and are expected to remain insulin dependent after TP-IAT.[22,29,30] Fibrotic histopathology, higher levels of pancreatic fat, and greater patient sarcopenia also have been associated with lower islet yields and a greater likelihood of insulin dependence postoperatively.[31-33] Importantly, in a multicenter retrospective trial, preoperative ERCP was not found to impact islet yield negatively during TP-IAT.[34]

Thus, to optimize outcomes related to opioid independence, and in particular insulin independence, patients should be referred before chronic changes, such as atrophy, calcifications, fibrosis, loss of islet mass, or other resectional or drainage pancreatic surgery is performed.[6] However, if the islet autotransplant ultimately fails and the patient's fasting C-peptide becomes undetectable, the patient may still be a candidate for pancreas or islet allotransplantation.[35-37]

Quality of Life

The main benefit of TP-IAT is improved QoL, which has been demonstrated consistently across a wide range of measurement tools.[8] Patients who undergo TP-IAT have increased quality-adjusted life years compared to those who undergo pancreatectomy alone.[1] More than 85% of patients reported improvements in all domains of health-related QoL in the range of 88% to 92% at 1 year. These improvements increased at 2 years and were sustained at 5 years post-TP-IAT.[8,24,38] QoL is correlated with insulin independence, lower HbA1c, and the presence of a functioning islet graft.[23] The present study was not designed to quantitatively or longitudinally assess QoL. Our understanding of QoL before and after TP-IAT would be enhanced by longitudinal qualitative research on this patient population.

CONCLUSIONS

Data from larger multicenter studies and the UW–Madison demonstrate that TP-IAT has the potential to alleviate pain, increase rates of insulin independence, and improve quality of life for patients with chronic pancreatitis or recurrent acute pancreatitis compared to pancreatectomy alone. Over the last decade, refined surgical approaches and improved patient selection further enhanced outcomes and decreased perioperative complication rates. Outcomes for TP-IAT patients at the UW are comparable to those at other centers in the US. Early referral of patients with CP and RAP to centers that perform TP-IAT can optimize islet yield at the time of islet isolation, thus maximizing the long-term benefit of the procedure. Therefore, we encourage an open dialogue between the providers who manage these complex patients and surgeons at centers that perform TP-IAT.

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