

# Current practices in islet cell autotransplantation

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REVIEW



## Current practices in islet cell autotransplantation

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### ABSTRACT

**Introduction:** Chronic pancreatitis and recurrent acute pancreatitis comprise a spectrum of disease that results in complications related to exocrine and endocrine insufficiency and chronic pain with narcotic dependence and poor quality of life. The mainstay of therapy has been medical and endoscopic therapy; surgery, especially total pancreatectomy, was historically reserved for few select patients as the obligate exocrine insufficiency and pancreatogenic diabetes (type 3C) are challenging to manage. The addition of islet cell autotransplantation after total pancreatectomy helps to mitigate brittle type 3c diabetes and prevents mortality related to severe hypoglycemic episodes and hypoglycemic unawareness. There have been more recent data demonstrating the safety of surgery and the beneficial long-term outcomes.

**Areas covered:** The purpose of this review is to describe the current practices in the field of islet cell autotransplantation including the selection and evaluation of patients for surgery, their preoperative work up and management, surgical approach, post-operative management and outcomes.

**Expert opinion:** Total pancreatectomy and islet cell autotransplantation has the ability to drastically improve quality of life and prevent brittle diabetes for patients suffering with chronic pancreatitis.

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## 1. Introduction

Chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP) caused by repeated inflammatory insults result in permanent damage to pancreatic gland causing scarring and damage to both the exocrine and endocrine cells of pancreas. This results in chronic and debilitating pain, exocrine insufficiency which can lead to malnutrition, and overall poor quality of life [1]. There are additional long-term risks including development of cancer within the pancreas and risk of progression to endocrine deficiencies, namely Type 3C or pancreatogenic diabetes. Because of the operative risks and morbidity as well as the potential for exacerbation of brittle diabetes, surgical management of this disease process (both for chronic pancreatitis and recurrent acute pancreatitis) is nuanced and benefits from an experienced, multidisciplinary team.

Management of these patients is complicated and includes management of both endocrine and exocrine insufficiency, physical and psychological issues (quality of life, chronic pain) and nutritional issues. The goals of management of CP are to prevent recurrent attacks of acute pancreatitis, relieve chronic pain, and improve quality of life, to prevent brittle pancreatogenic diabetes (Type 3C DM), and to avoid pancreas cancer. Medical and endoscopic therapies historically have been the first line of management. There are more recent data demonstrating the benefit of early surgical intervention [2]. Surgery for chronic pancreatitis includes partial resection, deemed parenchyma-preserving surgery. Examples of parenchyma-preserving operations include duodenum-preserving pancreatic head resection (Beger procedure), local

pancreatic head resection with longitudinal pancreaticojejunostomy (Frey procedure), pancreaticoduodenectomy (Whipple procedure), or distal pancreatectomy. The alternative to parenchymal-preserving operations is a total pancreatectomy (TP) with or without islet cell autotransplantation (IAT) [3]. The selection of the operation is based on surgeon and institutional preference.

TPIAT was first described in 1978 and has gained popularity mainly in the United States [4]. Recently, Collaborative Islet Cell Registry (CITR) has reported over 1000 cases performed over the last 15 years [5]. Currently around 30–40% of patients who present for evaluation of surgical management for CP vs RAP undergo TPIAT [3]. Perioperative management is not uniform [6]. The purpose of this review is to describe the current practices in the field of TPIAT including the selection and evaluation of patients for surgery, their preoperative work up and management, surgical approach, post-operative management and practices and outcomes. This review is based on generalized review of the literature and from manuscripts which describe accepted evidence-based practice in the field. It is not a qualitative systematic analysis; no database was used for this article.

## 2. Selection of patients for the surgery

When patients with CP and RAP are referred for surgical evaluation, the first step is to determine where the disease is dominant, and whether the pancreatic duct is affected in a way that requires a ductal drainage procedure or total pancreatectomy. The selection of the type of operation

**Article highlights**

- Surgical treatment in the form of total pancreatectomy for benign disease is often perceived as being radical, however the benefits outweigh the risks when paired with islet cell autotransplantation (both in terms of prevention of brittle diabetes and avoiding narcotic dependence).
- Success of TPIAT depends heavily on thorough evaluation, thoughtful patient selection, and cohesive multi-disciplinary management.
- Islet cell autotransplantation has been shown to avoid severe hypoglycemic episodes and hypoglycemic unawareness.
- Type 3C diabetes remains a poorly explored field in terms of research and clinical data reporting. Experiences from chronic pancreatitis centers will help to better understand this disease process.
- Future opportunities for basic and translational research include opportunities to maximize islet engraftment and growth into heterotopic tissues, as well as prevention of islet loss secondary to inflammation.

follows an algorithm previously published by our group [3]. In brief, if the dominant disease is in the head of the pancreas with severe ductal dilation, that patient is a candidate for a local pancreatic head resection with longitudinal pancreaticojejunostomy (Frey procedure). If dominant disease is in the head without ductal dilation, then either a pancreaticoduodenectomy (Whipple procedure) or duodenum-preserving pancreatic head resection (Beger procedure) is appropriate [3,7,8]. In patients with disease in the tail of pancreas, or in cases of a disconnected pancreatic duct, a distal pancreatectomy is selected.

In patients with diffuse disease, or if the patient has a genetic mutation that predisposes them to cancer, we consider them for total pancreatectomy with islet autotransplant (TPIAT) if their endocrine function is adequate (evaluation of endocrine function is discussed in the next section) [3,4,9–11]. Non-traditional indications for TPIAT include benign conditions such as pancreatic cystosis and borderline neoplasms such as intraductal papillary mucinous neoplasms (IPMN), mucinous cystadenoma, serous cystadenoma, solid pseudopapillary tumors, and neuroendocrine tumors [12,13]. Given the risk of liver metastases, islet autotransplant in this population has been controversial and has not been adopted by uniformly and done only at a few centers worldwide under research protocol.

### 2.1. Current practices in evaluation

The first step in evaluation is to determine the extent of parenchymal involvement. This is done with contrast-enhanced cross-sectional imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]). Our institutional preference is an MRI, as the degree of fibrosis can be used to predict islet cell yield. Evidence of fibrosis is suggested by abnormal signal on T1 weighted pre-contrast images, decreased pancreatic perfusion during the arterial phase, abnormal signal during the delayed interstitial phase, loss of parenchymal thickness and loss of acinar architecture on T2 weighted images [14]. Of the features evaluated during each of the MRI sequences, abnormal signal during the delayed

interstitial phase demonstrated the best correlation with islet yield [14].

Once the type of surgery has been selected, the next step in evaluation is to rule out malignancy. Any suspicious lesions identified on cross-sectional imaging are further investigated, typically by endoscopic ultrasound (EUS) with tissue sampling. Serum tumor markers including alpha fetoprotein (AFP) and cancer antigen 19–9 (CA19–9) are collected. As mentioned in the previous section, suspicion of malignancy or borderline malignant lesions is considered a contra-indication to TPIAT except at a handful of centers worldwide.

Portal vein thrombosis, either the main portal vein or segmental branches, following islet infusion remains a concern in the TPIAT population. As a result, many centers perform a hypercoagulable work up as a part of their selection process [6]. This includes obtaining a thorough history from the patient (to determine whether they have had any prior venous thromboembolism) as well as laboratory testing for Factor V Leiden, Protein C mutations, Protein S mutations, factor VIII deficiency, anti-phospholipid syndrome (including lupus anticoagulant, phosphatidyl serine, anti-cardiolipin, beta-2 glycoprotein), prothrombin gene mutation, MTHFR gene mutation, selenium, vitamin D-25 hydroxy, and homocysteine levels. Many programs including ours do not consider history of segmental splenic vein thrombosis as a result of chronic pancreatitis to be indicative of a hypercoagulable disorder.

Other components of the evaluation include performing age-appropriate cardiopulmonary testing to assess fitness for major abdominal surgery. Because of the chronic pain and narcotic usage in this patient population, a thorough risk assessment by a psychiatry and social work team is important. It is our practice to have patients evaluated by a dietician due to exocrine insufficiency in order to optimize patients prior to TPIAT.

### 2.2. Glycemic control

To ascertain an individual patient's ability to benefit from islet autotransplant, it is imperative to determine their baseline glycemic control. Traditional evaluation includes hemoglobin A1c, fasting serum glucose, fasting C-peptide, fasting insulin, and mixed meal tolerance [15]. Over the last few years, arginine- and glucagon-stimulated C-peptide and continuous glucose monitoring (CGM) have emerged as better than standard testing [16–18]. With regard to stimulated C-peptide testing and interpretation, fasting C-peptide is first collected. Another C-peptide level is drawn after stimulation with arginine or glucagon. The delta value is then interpreted. Oral glucose tolerance tests and mixed-meal tolerance tests are used to understand insulin resistance.

We use serum data (hemoglobin A1c and C-peptide levels) in conjunction with CGM. This is because the hemoglobin A1c provides a broad estimation of hyperglycemia but does not provide information about variability. Patients with chronic pancreatitis and episodes of acute recurrent pancreatitis can be subject to wide swings in their blood sugar. One aim of surgical management is to strive for insulin independence, but the greater threat to life is severe hypoglycemia and episodes of hypoglycemic unawareness. Data collected from CGM help

to understand their current glucose control and can be used to predict hyper- and hypoglycemia after resection. Under ideal circumstances, candidates for TPIAT will have CGM readings that demonstrate euglycemia 80% of the time. The remainder of their readings can vary between hyper- and hypoglycemia, but we prefer that no more than 20% of their readings are within hypoglycemic range. At our institution, the practice is to consider patients with a hemoglobin A1c <7%, stimulated C-peptide with  $\Delta \geq 2$  ng/mL, and CGM readings with no more than 20% of time in hypoglycemic range for TPIAT. Recently, there have been reports that have demonstrated that TPIAT can be performed in patients with borderline DM or DM who demonstrate beta cell response on stimulated C-peptide [3,19].

### 3. Surgery

One of the principles of surgery to optimize islet yield is the preservation of vascular inflow to the pancreas during the dissection phase of the operation. This prevents gland ischemia and minimizes islet loss [20]. Another technique that has been shown to minimize islet loss is removal of the gland in its entirety, as opposed to dividing the pancreas (typically at the neck) and removing it in pieces. Whole specimen removal is thought to be superior as it avoids the inflammation associated with dividing the pancreas in situ [21].

Minimally invasive approaches to pancreatectomy, either through laparoscopic or robotic platforms, have been described [22–24]. As expected, operative time tends to be longer in either laparoscopic or robotic TPIAT as compared to open procedures [22,24]. Current data report that parameters including postoperative narcotic use, length of stay, and patient-reported quality of life are no different between laparoscopic and open TPIAT, but this may continue to evolve as surgeons overcome the steep learning curve associated with these platforms.

#### 3.1. Islet cell isolation

Once the pancreatectomy has been completed, the gland is sent for the isolation procedure. Non-essential tissues (including connective tissue, surrounding fat, the duodenum, vascular supply) are removed and the pancreas is washed in an antibiotic solution. The pancreatic duct is cannulated and infused with an enzymatic solution to aid in digestion. The pancreas then undergoes mechanical digestion, most commonly in a device called the Ricordi chamber. The islet cells are isolated and purified and final product yield is analyzed for volume and viability [20].

#### 3.2. Islet cell administration

The most common route of delivery of islet cells is by intraoperative portal vein infusion. Our institutional practice is to cannulate the splenic vein stump. Prior to infusion, portal pressure is measured. Infusion is then initiated. Portal pressures are rechecked every 3 min and infusion is paused for any pressure measurements over 25 cm H<sub>2</sub>O. Selected centers infuse the islets percutaneously with the assistance of

interventional radiologists. This shortens the operative time, as patients can wait in the intensive care unit during the isolation process, but increased vascular complications including hepatic artery pseudoaneurysm and portal vein thrombosis [25].

### 4. Immediate post-operative care

The immediate post-operative care of patients after TPIAT occurs in the surgical intensive care unit (SICU) as it involves close hemodynamic monitoring, hourly glucose checks, fluid resuscitation [26]. Patients are typically left intubated for the first night after surgery. Fluid resuscitation is aimed at euolemia. At our institution, patients have central venous catheters, and the central venous pressure (CVP) is used to guide resuscitation along with standard vital parameters including hemodynamics and urine output. Serial labs are obtained.

Management of anticoagulation after TPIAT involves the balance of risk of bleeding after major surgery and dissection with the risk of portal venous thrombosis as a result of islet cell infusion. Other factors such as hypercoagulable disorders and instant blood-mediated inflammatory response (IBMIR) may predispose patients to thrombosis. There is no standard protocol for anticoagulation for all patients undergoing TPIAT. Approximately one-third of centers report obtaining a hypercoagulable work up prior to surgery, while others classify patients as high risk for thrombosis based off any prior history of thrombotic events [6]. Most programs use a heparin infusion in the first 24–48 h after surgery, titrated by activated partial thromboplastin time (aPTT) or anti-Xa levels [27]. Over the course of their hospital stay, most patients are transitioned from the heparin infusion to prophylactic doses of either low molecular weight heparin (LMWH) or subcutaneous heparin, typically continued for 2–4 weeks post-operatively [6]. Incidence of bleeding requiring transfusion or unplanned return to the operating room was relatively low (6.6%) in an international survey conducted among islet transplant programs. Incidence of portal vein thrombosis was reported to be zero in a recent multicenter study [6]. It is the practice at our institution to obtain duplex ultrasounds of the liver to confirm portal vein patency at serial intervals after surgery (post-operative days 1, 2, 5).

TPIAT is typically accompanied by splenectomy, making post-splenectomy reactive thrombocytosis a common feature. Studies have reported evidence of thrombocytosis occurring at median post-operative day 8, peak platelet count median post-operative day 20 [28]. Reactive thrombocytosis is self-limited. There is heterogeneity in practice; approximately one-third of adult centers report treating with aspirin [6].

The purpose of islet autotransplantation versus total pancreatectomy alone is to avoid brittle diabetes associated with loss of islet cells, often referred to as Type 3C [29]. In the early post-operative period, the aim is to optimize islet recovery and engraftment. Ultimately, success is highly dependent on islet cell mass. An insulin infusion is started on post-operative day 0 to maintain euglycemia. Insulin infusions are titrated to maintain blood sugar between 80 and 120 mg/dL [26,30]. Once patients are tolerating enteral feeds, the infusion is transitioned to a combination of short- and long-acting

subcutaneous insulin. The University of Minnesota group has published on their experience using closed-loop therapy using an insulin pump and continuous glucose monitor (CGM). They reported that this closed-loop therapy group had significantly lower mean blood glucose concentrations without any difference in hypoglycemia [31]. Regardless of the modality, tight glucose control using exogenous insulin is thought to reduce stress on the islet cells in order to promote engraftment [32].

## 5. Long-term management

### 5.1. Endocrine management

Exogenous insulin is continued as an outpatient, titrated to euglycemia. There are data to support tighter glucose control in TPIAT patients with a goal hemoglobin A1c <6.5% in order to minimize islet damage from hyperglycemic stress [33]. This is felt to aid in islet engraftment to give patients the best possible chance at insulin independence. At our center, patients are followed by the surgical team, pharmacy team, and endocrinologists who specialize in pancreatogenic diabetes. Ultimately, only one-third of patients after TPIAT will achieve insulin-independence [34,35]. However, insulin independence should not be perceived as a sole marker of success for these patients. The main objective is to alleviate pain, improve quality of life and prevent the brittleness of diabetes, in which this procedure doubtlessly achieves objectives. Patients typically perform home blood glucose checks and are monitored with fasting blood glucose and hemoglobin A1c in the clinic setting on a regular basis [9]. As discussed above, continuous glucose monitoring (CGM) has been used in the TPIAT population to trend both hyper and hypoglycemia. This is a useful adjunct in management, especially to aid in detection of potentially life-threatening hypoglycemia [30,36]. The use of CGM has been demonstrated to provide accurate glucose levels on multiple studies, and out-performs traditional home glucose testing with regard to patient-reported satisfaction [18,30,31,37].

The use of non-insulin antihyperglycemics have been studied in preclinical animal models of TPIAT. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) increase insulin secretion and improve beta cell health by promoting proliferation and inhibiting beta cell apoptosis [30,38]. The use of a GLP-1 receptor agonist prior to islet cell transplant has been shown to improve islet function and glucose homeostasis in mouse models [39,40]. Other groups have studied the effects of inhibiting dipeptidyl peptidase-4 (DPP-4, the enzyme which degrades GLP-1), on outcomes. This has not been demonstrated to improve glucose control as measured by mixed meal tolerance tests in patients following TPIAT [41].

### 5.2. Pain management

Mechanisms for chronic visceral pain in patients with CP and RAP are multifactorial and not fully understood [42]. Many patients are opiate-dependent prior to surgery, with rates of daily opiate use often quoted above 80% [30,34,42,43]. A recent meta-analysis of patients undergoing TPIAT found

opiate use to be decreased in all pooled studies with an opiate-free rate of 63% at 1 year follow-up [34]. For patients who do not achieve opiate independence, the majority still report improvements in physical and mental health quality of life at 1 year [34,42,43].

### 5.3. Exocrine management

All patients will have exocrine insufficiency after TPIAT. The use of lifelong pancreatic exocrine replacement therapy has been demonstrated in clinical studies and is supported in the most recent published consensus guidelines [9,44,45]. Patients should be screened regularly to monitor for malabsorption, vitamin deficiencies, and malnutrition. Patients should be asked about weight loss, diarrhea or other symptoms of steatorrhea. Weight should be measured at each clinic visit. Nutrition labs, including albumin, pre-albumin, and fat-soluble vitamins, can also be used for guidance [9].

### 5.4. Health maintenance

Rates of splenectomy during pancreatic resection vary by institutional practice, as well as by the extent and location of disease (for example, pancreatic head resections may not require routine splenectomy) [46]. In situations where splenectomy is expected, patients should receive vaccines against the encapsulated bacteria *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis* 2 weeks before surgery [30]. The pneumococcal vaccine requires an additional dose 5 years after the first, and meningococcal vaccines are administered every 5 years [47]. Patients should also receive the influenza vaccine seasonally [47].

## 6. Expert opinion

TPIAT is an important tool in the armamentarium of treatment options for chronic and recurrent pancreatitis. Type 3C DM remains a major concern with the potential for severe hypoglycemic episodes and hypoglycemic unawareness. As a result, total pancreatectomy is often perceived as a radical procedure for a benign disease. The risks associated with surgery and with long-term diabetes care must be balanced against the risk of narcotic dependence, psychological issues, and risk of suicide in these patients in the absence of surgery cannot be overlooked. Islet cell autotransplantation has demonstrated success in various studies about its ability to offer greater quality of life and prevention of brittle diabetes. It is our opinion that TPIAT offers hope to patients suffering with chronic pain and poor quality of life. The ongoing opiate epidemic highlights the possibility of narcotic dependence and misuse for individuals with chronic pain. For patients who do not achieve or sustain insulin independence, advancements in endocrinology including CGM and novel glucose lowering therapies (including medications such as GLP-1 agonists) are valuable adjuncts to patients after TPIAT. Success of TPIAT programs depends on a dedicated multi-disciplinary team to shepherd patients through the preoperative work up and evaluation, the surgery itself, and long-term post-operative management.

The next advances in the field of chronic pancreatitis and islet autotransplantation will likely be made in the basic and translational research space. Currently, TPIAT addresses quality of life-related outcomes, but as a field we have not yet achieved insulin independence for the majority of patients. Transplanted islets struggle to engraft in heterotrophic tissue and suffer islet loss, both in the immediate postoperative period and over time. This is due to the instant blood-mediated inflammatory response, hypoxic environment, and altered pathology of liver (especially in circumstances of hepatic steatosis). All of these factors increase the inflammatory response which results in loss of islet cells and decreases their ability to regenerate [48]. Biological agents are used to curtail the inflammatory response [30]. Pre-clinical small animal models have demonstrated some efficacy with islet cell transplantation into skeletal muscle, peritoneum, or omentum aimed to improve islet survival given their vascularity and large surface area; however, liver still remains the most practical and suitable site for transplantation [49,50]. Investigation of medications that can promote islet survival and decrease islet apoptosis, as the GLP-1 receptor agonists and DPP-4 inhibitors will be important. Transplantation of mesenchymal stem cells (MSC) along with islets for potential future multiplication and growth of these cells or hypothesis of co-transplanting MSC derived products may bring impactful results in future [51].

As the understanding of type 3C diabetes grows, indications for TPIAT may be expected to increase to include patients with well-controlled diabetes or pre-diabetes with adequate insulin secretion. These individuals may still benefit from the total pancreatectomy with regard to their pain control, and avoid brittle diabetes and resultant hypoglycemia. While there are patients who do not sustain insulin independence, their glucose control tends to be manageable, and they are still able to experience benefits in terms of chronic pain. Advancement in the field of endocrinology in regards to sophisticated insulin pumps will help endocrinologists manage these patients when insulin independence is not achieved. Currently, there are not many centers in the country with the resources to sustain TPIAT programs. Management of patients with chronic pain, endocrine and exocrine insufficiency from CP is inherently challenging. We have found that a dedicated multi-disciplinary approach is essential to identify which patients can benefit from TPIAT. It is our hope that awareness in the community about TPIAT grows. This will allow patients who are suffering with chronic pancreatitis or recurrent acute pancreatitis to be referred to centers performing TPIAT so that these patients have access to therapy that can dramatically improve their quality of life.

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