

The Role of Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis

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Total pancreatectomy (TP) or near-total pancreatectomy with islet autotransplantation (IAT) to treat chronic pancreatitis (CP) first was done in 1977 at the University of Minnesota (UMN) and described in *Surgical Clinics of North America* [1]. The idea evolved from a desire to compare metabolic outcomes between islet autografts in pancreatectomized individuals, who could not reject their graft, and islet allografts done to treat type 1 diabetes, to understand why the latter failed (was it for technical or immunologic reasons?) [2]. The main rationale from the beginning, however, was to relieve the pain of CP in patients in whom other measures had failed and, to preserve beta (β)-cell mass and insulin secretory capacity, to prevent or minimize the otherwise inevitable surgical diabetes [3].

Although IATs have been done with pancreatic resections for premalignant neoplasias, and for acute relapsing pancreatitis (ARP) before evolution to CP occurs, the major application of TP-IAT has been in patients who

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have CP and intractable pain [4]. TP, even with IAT, may appear to be a radical treatment, but for the CP patients in whom it is done, the alternative is even more radical: persistent pain and/or lifetime narcotic use. Thus, an appreciation of the spectrum of the disease, the possible lack of correlation between imaging or gross pathology results and the degree of pain, and the various mechanisms by which CP causes pain are relevant for patient selection and interpretation of outcomes in the TP-IAT series reviewed here.

Brief review of chronic pancreatitis and treatment options

CP is characterized by progressive, irreversible damage to the pancreas, with varying degrees of inflammation, fibrosis, ductal alteration, exocrine atrophy, and secondary involvement of the islets of Langerhans. The clinical manifestations also vary as to the degree of pain, maldigestion from loss of exocrine function, and occurrence of diabetes. Although lost exocrine function can be managed with oral pancreatic enzyme supplements, and diabetes, if it occurs, with insulin, the hallmark of CP is pain, often intractable and debilitating. Pain is the main symptom toward which therapies are directed, all with significant failure rates.

The acute and chronic forms of pancreatitis are not totally distinguishable. They have overlapping risk factors and share a common pathogenetic origin as a pancreatic autodigestive process. Additionally, they each may manifest as an initial episode of abdominal pain, with elevation of serum amylase and lipase, and with similar nonspecific inflammatory changes. CP is likely the result of progressive pancreatic damage after recurrent episodes of pancreatic necroinflammation. The sentinel acute pancreatitis event (SAPE) hypothesis, introduced by Schneider and Whitcomb [5], postulates that the sentinel event is a pancreatic injury that makes the gland particularly vulnerable, in the recovery phase, to additional insults such as alcohol, metabolic, and oxidative stresses. ARP may evolve to CP; patients who are initially pain free between episodes may begin to have underlying interval pain and may cease having episodes altogether. Even one episode of acute pancreatitis may be followed by evolution to CP, or CP may occur without a history of an identifiable episode of acute pancreatitis. Whatever the trigger, progression of CP to end-stage fibrosis occurs at different rates in different people, and can be caused by different mechanisms [6].

Traditionally, alcohol abuse has been thought to be the cause of most cases of CP, but this perception may not be correct. Indeed, in the TP-IAT group at UMN, only 16% of the cases of CP were attributed to alcohol, and 60% were idiopathic [7]; in the series at the University of Cincinnati, only 4% of the cases of CP were attributed to alcohol [8]. Cigarette smoking is also a major risk factor for CP [9,10]. Well-defined inherited germline mutations also can cause CP in families [11]. Hereditary pancreatitis once was thought to be rare, diagnosed only when other family members

are affected. The identification of PRSS1, SPINK1, and CFTR mutations in patients with so-called idiopathic CP, however, indicates that genetic risk factors are much more common than originally envisioned [12]. These mutations have both autosomal-dominant and recessive patterns of inheritance with variable penetration and may be influenced by certain modifier genes and environmental factors. The discovery of SPINK1 mutations in various types of CP, such as tropical calcific, alcoholic, and autoimmune pancreatitis, blurs the borders between the particular CP subtypes [12–14]. Other risk factors for CP include biliary lithiasis, anatomical variants like annular pancreas or divisum, hypertriglyceridemia, hypercalcemia, sphincter of Oddi dysfunction, and trauma [7,8,12]. The key histopathologic features of CP, regardless of the etiology, are varying degrees and combinations of pancreatic fibrosis, acinar atrophy, acute and chronic inflammation, and distorted or blocked ducts.

The diagnosis of CP is based mainly on symptoms, imaging studies, and supporting laboratory tests. In certain patients, the diagnosis can be surprisingly difficult, especially in those who have early or mild small-duct or minimal-change variants [15,16]. Serum amylase and lipase levels typically are elevated during attacks early on but might be normal in later phases with progressive destruction of the gland. Imaging studies include CT, endoscopic retrograde cholangiopancreatography (ERCP) (which is associated with a risk of precipitating pancreatitis), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) [17]. Although all of the studies can detect ductal and textural abnormalities, the specificity and sensitivity of each in diagnosing CP are not defined well, given the difficulty of obtaining histopathologic correlation.

The treatment of patients who have CP is focused on mitigating their unrelenting or recurring abdominal pain. Patients who imbibe alcohol or smoke should stop. Pancreatic enzyme supplementation may help. Non-narcotic analgesics should be tried first, but many need narcotic analgesics; patient comfort takes precedence over concerns of addiction [18–20]. Some patients need escalating doses, with the addition of fentanyl patches or even parenteral administration. Celiac ganglion blocks, percutaneous or endoscopic, can be tried but rarely give permanent pain relief, if any at all, and transient responses often cannot be repeated [21]. Patients who require narcotic analgesics, with or without complete relief, are candidates for invasive procedures in an attempt to remove or modify the root cause of the pain. The general progression is from the least to the most invasive procedure, depending on the response.

Pain in CP occurs with or without ductal obstruction. When obstruction, increased intraductal pressure, or a dilated duct can be demonstrated, efforts should be made to relieve the obstruction. If pain persists or recurs, then the next step is pancreatic resection. Because previous surgical drainage procedures (Puestow or Berger) compromise islet yield if a subsequent TP-IAT is done [7], the current UMN paradigm is to do any indicated drainage

procedures endoscopically only. Then, if the endoscopic drainage is unsuccessful, the authors proceed to resection rather than surgical drainage. Although two randomized trials of highly selected subgroups of patients who had severe CP cases showed that primary surgical drainage had a better chance of relieving pain than endoscopic drainage [22,23], most gastroenterologists, because it is minimally invasive, advocate an initial trial of endoscopic therapy in an attempt to relieve pain in patients who have a dilated duct, stricture, or pancreatic stones [24]. If endoscopic drainage fails, there is little evidence that surgical drainage will be successful in relieving pain. As primary therapy, each approach has a relatively high failure rate; pain persisted in 68% of patients who had endoscopic and 25% who had surgical drainage in the study by Cahen and colleagues [23]. Even in those who have initial relief following either endoscopic or surgical drainage, it may not be sustained longer than 5 years.

The ideal CP candidates for endoscopic drainage procedures have a focal proximal stricture associated with upstream dilation of the pancreatic duct, or relatively small burden of main pancreatic duct stones that is amenable to extraction with or without extracorporeal shock wave lithotripsy, or a pseudocyst. Endoscopic therapy most often is successful in patients who have moderate disease. Successful treatment of strictures requires aggressive therapy, with repeated dilations and stenting in hope that the stricture resolves. There is wide variability in expertise, aggressiveness, and conceptual approaches to endoscopic therapy, which may influence outcomes [19,24]. Although the complication rate of endoscopic therapy is relatively low, acute episodes of pancreatitis can occur after sphincterotomy and stent placement, and in some patients, the underlying pain becomes worse; such patients are prime candidates for resection, including TP-IAT.

Pancreas resection is indicated in CP patients who have small-duct disease or those in whom endoscopic drainage fail. A TP is the most likely operation to relieve pain, and for CP patients who are already diabetic, there is little reason not to do it. For nondiabetic CP patients, a TP-IAT reduces but does not eliminate the risk of surgical diabetes. Thus, a case can be made for partial resection (usually a Whipple operation, but a distal pancreatectomy for the rare case with a mid-duct stricture and CP of the body and tail only). If pain is not relieved by a partial resection, a completion pancreatectomy with IAT can be done subsequently.

Patients tend to be referred for resection late in the course of CP, often with a pain history of years, and many opt for TP rather than a partial resection, wanting the best chance at pain relief without the risk of reoperation. TP-IAT done early in the course of CP avoids the complications of chronic narcotic use and gives the best chance at a high islet yield to prevent or minimize postpancreatectomy diabetes.

The authors' experience indicates that TP with preservation of β -cell mass by immediate isolation and intraportal transplantation of islets from the excised pancreas should be considered as a primary surgical option

for patients who have painful CP refractory to less invasive procedures. The main criterion for success of the islet autograft per se is whether insulin independence is maintained or surgical diabetes made milder. The overall outcome, however, depends as much on the clinical response as on the metabolic results, specifically whether the patient's pain is reduced or eliminated, narcotic analgesics withdrawn, and the quality of life (QOL) improved.

Historical context

The first patient in the UMN series (and the world) to undergo an IAT after pancreatectomy [1], in 1977, remained insulin-independent and pain-free until she died 6 years later [25]. This case proved that a viable islet preparation could be made from a freshly excised human pancreas. It also showed that the previous failures with islet allografts were caused either by low viability or poor preservation of deceased donor pancreases, or rejection [26].

As of early 2007, the UMN IAT experience includes more than 200 cases, and the outcomes of the first two thirds have been published [1–3,7,25–35]. Shortly after the initial reports on IATs from the UMN nearly 30 years ago [1], several other centers worldwide began to do the same. To date, at least 20 centers are known to have done IAT, nearly all by embolization of the isolated islets to the liver by means of the portal vein (Fig. 1). The world

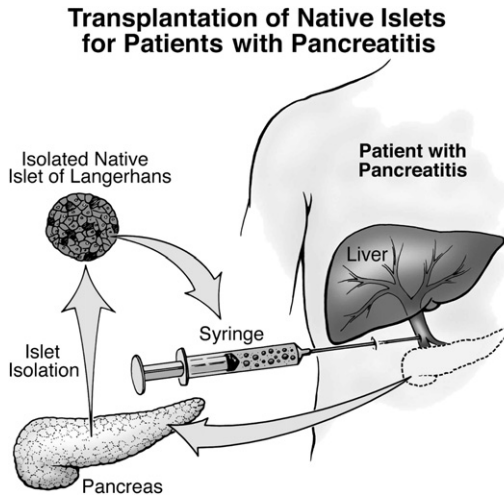


Fig. 1. Sequence of events to preserve β -cell mass in patients undergoing a total pancreatectomy for benign disease. The resected pancreas is dispersed by collagenase digestion followed by islet isolation. Autologous islets then are embolized to the patient's liver by means of the portal vein.

literature as of 2006 contains reports of about 300 IATs, including the UMN cases cited previously and those done elsewhere [8,36–45]. After UMN, the next largest series are at the University of Cincinnati (nearly 100), the University of Leicester (more than 40), and the University of Geneva (more than 20).

For historical completeness, segmental pancreatic autotransplantation is mentioned as another method for preserving β -cell mass after pancreatic resection [46–48]. The first such case was done around the time of the first IAT [46]. This approach appears to have been used less frequently than IAT; indeed, no reports have appeared in the literature on segmental pancreas autotransplants for the past decade.

Patient selection and pain syndrome

The severity of the gross morphologic changes associated with pancreatitis, as detected by imaging studies, do not correlate necessarily with the degree of pain the patient is experiencing [49,50]. Minimal change CP was first described by Walsh and colleagues [15] in patients who had severe abdominal pain with minimal gross morphologic changes but clear histopathologic changes in the gland, with resolution of pain in most patients following pancreatectomy. Layer and colleagues [16] also described two forms of CP: early-onset CP, where pain precedes by years the development of gross pathologic changes, and late-onset CP, where gross changes are already detectable by the time the patient has pain. These two articles were published before the EUS era.

Ideally, EUS should allow minimal change CP to be detected, but because it is standard to require that five of the nine features tested for on EUS (hyperechoic parenchymal foci, strands, hypoechoic lobules, cysts, main duct irregularity, ductal dilation, hyperechoic duct walls, visible side branches, and calcifications or stones) be present for a diagnosis of CP to be made to avoid overcalling [50], the minimal change variety may be present but not diagnosed. In 15 patients of the authors' series in which recent EUS findings could be correlated with pancreatic histopathology following resection (CP confirmed in all), seven had minimal change CP with only mild fibrosis. Five had fewer than EUS criteria for CP, yet all had inflammation present (including one with no features of CP detected on EUS) [51]. Further support for the contention that the current criteria, designed to prevent overdiagnosing CP on EUS [50], may underdiagnose comes from Chong and colleagues [52] at the Medical University of South Carolina. They found that a threshold of three criteria gave the best balance between sensitivity (83%) and specificity (80%) for correlation of EUS findings with histological CP. Thus, patients who have an abdominal pain syndrome who have any one of the nine features consistent with CP on EUS may indeed have the disease, probably in the minimal change category. The authors know of no report in

the literature that correlates the severity of pain and the morphologic findings of radiologic or pathologic studies.

The pain of pancreatitis is multifactorial [53–55]. Even when there is increased ductal pressure, it is not necessarily the cause of the pain [56], and pain in patients who have CP exists in the absence of increased ductal pressure. Indeed microscopic pathology with intrinsic neuritis had the best correlation in at least one study [53]. Some patients have increased sensitivity to pain of central origin, perhaps explaining the symptoms in minimal-change CP [57].

Thus, at UMN, the authors do TP-IAT in CP patients who have intractable pain, whether the gross morphologic changes detected in the pancreas are minimal or severe. It is almost always worth an attempt at islet isolation, because having even a small β -cell mass is better than having none. Occasionally, and especially in CP patients who already have impaired glucose tolerance, the pancreas is such a small atrophic rock that the authors make a decision not to go to the expense and effort of an islet isolation that is almost certain to be ultra-low.

Patients who have ARP are also candidates for TP-IAT if their episodes are frequent, disruptive, and persist over time, even if they are pain-free between episodes. Evolution of ARP into CP, where elevated levels of serum amylase and lipase cease but pain persists, is common and often misunderstood as meaning the pain is other than pancreatic. In nondiabetic patients requiring narcotics for their pain who have a history of ARP associated with even minimal criteria for CP on imaging studies, the authors recommend TP-IAT [32].

Some patients who have CP have diabetes when referred for surgical consultation. In such patients, the decision for resection is easy, especially when exocrine deficiency also exists. Most patients, however, are seen when diabetes does not exist, and thus a TP must be undertaken with the acceptance of diabetes as a tradeoff for pain relief and for the chance to discontinue narcotics. If an IAT prevents diabetes, it is a bonus. When a TP is done for CP in a nondiabetic patient, however, an IAT to preserve β -cell mass should be done whenever possible.

Surgical resection considerations

During TP, the blood supply to the pancreas should be preserved as long as possible to minimize the detrimental effects of warm ischemia on the islets [27,58,59]. To do so, never separate the distal pancreas from the splenic vessels. If the splenic vessels are ligated in the hilum, the spleen may survive on its collateral vessels, but usually it has to be taken. When the spleen is spared, there is a risk of variceal formation in the gastric veins draining the spleen leading to late intestinal bleeding, or splenomegaly that can be painful, so the authors leave it only if retains an absolutely normal appearance after hilar ligation.

At UMN, early IAT series included cases with the entire duodenum preserved (95% pancreatectomy), but the complication rate was actually lower in patients who had part of the duodenum or the entire duodenum resected [25]. For the past 15 years, the authors have done a pylorus- and fourth portion-sparing partial duodenectomy when possible, with orthotopic reconstruction by means of duodenostomy and choledochoduodenostomy (Fig. 2).

Metabolic considerations

In patients who have painful CP referred for resection, baseline metabolic studies to assess β -cell function include fasting and postprandial glucose, baseline and stimulated C-peptide, and glycosylated hemoglobin levels. Patients who have CP often have symptoms of exocrine insufficiency (steatorrhea), but formal evaluation usually is not done. IAT candidates are counseled that exocrine deficiency may be made worse or induced by TP.

Although the authors sometimes try to spare the proximal and distal duodenum during TP, data from the bariatric literature suggest that there may be a metabolic benefit of duodenectomy. GLP-1, produced by L cells in the distal intestinal tract is a powerful incretin. Patients who have a Roux-en-Y gastric bypass have increased levels of GLP-1 with improvement in diabetes, results not seen after restrictive bariatric procedures [60,61]. It is possible that complete duodenectomy at the time of TP would increase GLP-1 levels and mirror the positive impact on insulin sensitivity seen in the bariatric duodenal bypass patients, allowing a reduced islet mass to sustain insulin independence.

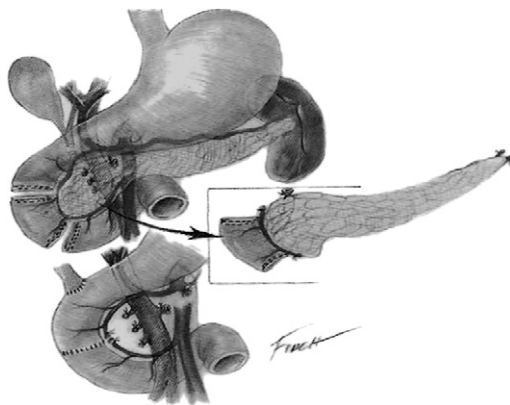


Fig. 2. Surgical technique for total pancreatectomy. Total pancreatectomy and pylorus- and distal-sparing duodenectomy with orthotopic reconstruction by means of duodenostomy and choledochoduodenostomy. (Adapted from Farney AC, Najarian JS, Nakhleh RE, et al. Auto-transplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. *Surgery* 1991;110(2):427–37 [discussion: 437–9]; with permission. Copyright © 1991, Elsevier.)

Islet isolation and infusion considerations

In the United States, islet isolation must be done in a laboratory that meets all of the US Food and Drug Administration (FDA) criteria for processed tissue. Only a few medical centers currently have such a laboratory.

After resection, the pancreatic duct is cannulated, and the pancreas is dispersed by collagenase digestion, using the modified Ricordi technique [34,35]. At UMN, the authors do not purify preparations with a low tissue volume to maximize the islet yield [62]. If the crude tissue digest exceeds 15 mL, the authors usually reduce the volume by purifying all or part of the islet preparation, so that embolization to the liver occurs without any undue rise in portal pressure [63,64]. If portal pressure reaches 20 to 30 cm of water, the residual preparation can be dispersed freely in the peritoneal cavity or transplanted beneath the kidney capsule, or submucosal layer of the stomach, in the hope that the islets engraft [28,65]. The authors' current preference is to purify islets so that the tissue volume is reduced to an amount tolerated by the portal vein, without any undue rise in pressure, but not to the degree that a large number of islets have to be discarded or placed in alternative sites. Sometimes the authors do not purify a high-volume digest, because a high percentage of the islets are mantled by, or not cleaved from, a surrounding rim of exocrine tissue, and we will lose most by purification.

Clinical observations and animal studies indicate that the liver (by means of the portal vein) is the most efficient site for islet engraftment [28,66,67]. Other sites used, such as the renal capsule [68–71], spleen [67,72], omentum [73], and peritoneal cavity [74,75] rarely have been associated with function of islet autografts in people [76,77]. At any site, the islets initially survive by nutrient diffusion; during this period, they have reduced functional capacity, with function improving once neovascularization occurs [78,79].

To prevent intraportal clotting from the tissue thromboplastin (present in the islet preparation) [80], the authors have administered heparin since their first cases in the 1970s [2,28]. Nearly all of the reports of complications related to portal infusion of islets [80–83] were published before the standardized semiautomated pancreas dispersion techniques and before the routine use of heparinization at all centers.

In islet allograft recipients, one study by Doppler ultrasound showed a 4% incidence of radiologically detected but clinically insignificant portal vein thrombosis [63]. In the authors' IAT series, portal vein thrombosis occasionally is detected on ultrasound, but not as a clinical entity. The authors always administer heparin before islet infusion and continue the infusion for a few days if the closing portal pressures are high. Liver function tests typically show a transient rise in serum enzyme levels during the early postoperative period [35], with no implication for future hepatic dysfunction.

Intra- and postoperative considerations

The authors maintain euglycemia by an insulin drip during and after the pancreatectomy and IAT [84]. Animal studies have shown a decrease in islet engraftment with hyperglycemia; furthermore, glucose toxicity may cause dysfunction and structural lesions in the transplanted islets [85–88]. The authors promote islet engraftment by an exogenous insulin drip to maintain euglycemia, minimizing insulin secretory demand from the freshly infused islets. A transition to subcutaneous insulin is made when the patient begins to eat, with the dose again adjusted to maintain euglycemia; insulin gradually is withdrawn in patients who can achieve euglycemia without it.

Expanding application

IATs have been done after resection for benign pancreatic processes, including pancreatic pseudocysts [43], cystic neoplasms [89,90], insulinomas [90,91], and a neuroendocrine tumor [90]. In each case, pathologic evaluation was completed before the IAT to confirm that the lesions were benign.

In the UMN series, IATs have been done at the time of distal pancreatectomy for benign cystic tumors in five patients (unpublished observation). In these cases, the authors are uncertain how well the intrahepatic islets are functioning, because those in the native pancreatic remnant also are functioning. The authors' series also includes a few CP patients whose IATs were done after only a distal pancreatectomy, with the head remaining. When a completion pancreatectomy was later done, diabetes was prevented, indicating good engraftment at the initial IAT (unpublished observation).

An IAT also has been reported in a patient with pancreatic adenocarcinoma who had a Whipple operation complicated by an anastomotic leak at the pancreaticojejunostomy. The leak was treated by an urgent completion pancreatectomy with an IAT [92]. The risk of doing an IAT when a completion pancreatectomy is done because of a technical complication of a Whipple procedure cannot be calculated from one case, but conceptually the procedure is valid, because the judgment must be that the distal pancreas was tumor-free by leaving it in (otherwise a Whipple operation would not have been done). A case also could be made for doing a TP-IAT, even in situations where a Whipple otherwise would suffice, but where a TP would be safer by avoiding an enteric anastomosis to a soft pancreas that has a higher than average leakage or breakdown probability.

Transplants of islets isolated from pancreas allografts excised for technical problems or allograft pancreatitis (islet auto-allografts) also have been performed, with one case published by the authors [93]. This patient remained insulin-independent for more than 1 year while on immunosuppression, but ultimately needed exogenous insulin from decline or loss of islet function for immunologic or nonimmunologic reasons. Additionally, most

of the other islet auto-allografts have had limited duration of function (unpublished observation).

Islet autotransplantation in children

CP is less common in children than in adults, but should be treated with the same aim: to relieve pain, eliminate the need for narcotics, and preserve β -cell mass. As of December 2006, the authors performed 25 IATs in children; the youngest was 5 years old. The authors reported their first pediatric case in detail [94]. In a subsequent report of their initial cases, the authors had a 50% rate of insulin independence [32]. In the authors' most recent long-term follow-up of 18 pediatric patients, more than 60% had discontinued narcotics, with a 78% rate of full or partial islet function and a 54% rate of insulin independence at 1 year [95].

Literature review

The largest series published to date on patients undergoing pancreatectomy and IAT have come from UMN [1–3,7,25,27,28,32,34,35], the University of Cincinnati [8,37], and the University of Leicester [43–45]. Reports have focused on metabolic outcomes, QOL, and pain reduction.

Insulin independence

The ability to achieve insulin independence after IATs appears to correlate directly with the islet equivalents (IEs) infused. IEs serve as an indirect measurement of β -cell mass, but there is much overlap, in that a small percentage of patients receiving less than 2000 IE/kg will become insulin-independent, while some receiving more than 5000 IE/kg will not [7,8]. The authors have shown that islet yields are poorest in patients who have prior pancreatic resections (distal pancreatectomies or surgical drainage procedures such as the Puestow procedure) [34,96]. In addition, fewer islets are recovered as pathologic fibrosis increases [28,34]. The timing of the procedure has a direct impact on islet yield. Maximal islet yield and insulin independence may be attained more easily if the IAT is performed earlier in the disease course, as recently reported by the Cincinnati group [18,37].

University of Minnesota series

In the authors' 1995 report [28], the lowest islet yields were in patients who had a prior Puestow procedure, with only an 18% rate of insulin independence in this group, in contrast to 71% in patients without a prior resection or drainage procedure. In a later update of the UMN series, at a time

when the authors were much more likely to treat even mild hyperglycemia, and nearly all patients underwent a TP, insulin independence was achieved in only 16% of patients with prior resections versus 40% in those without prior resections [34]. A prior Whipple operation had less effect on the islet yield than a distal pancreatectomy [32].

As of December 2006, 198 IATs had been done at the UMN, more than half of them since 2000 (Fig. 3). A recent analysis involving 188 patients (unpublished data), whose TP-IATs were done between February 1977 and September 2006, showed a patient survival rate of 98% at 1 year and 73% at 10 years, with complete pain relief or reduction in over 90% of patients and discontinuation of narcotics in half. In addition, 55% of adult patients had full islet graft function and were insulin-independent at 1 year after transplant. A third of the patients were insulin-independent at 10 years, and another third had partial islet function with minimal insulin requirements.

The authors' latest published outcome analysis included 136 patients cared for from 1977 through 2004; of those, 120 had sufficient follow-up for analysis [7]. The age range was 5 to 70 years old (Fig. 4); duration of disease was 1 to 30 years (Fig. 5). The etiology of CP was idiopathic in 43% of the patients (Box 1). Most had had previous operations, 33% directly on the pancreas. Previous operations included:

- Abdominal operations—126 (93%)
- Cholecystectomy—57 (42%)
- Pancreatic operations—45 (33%)
- Puestow—17
- Duval—1

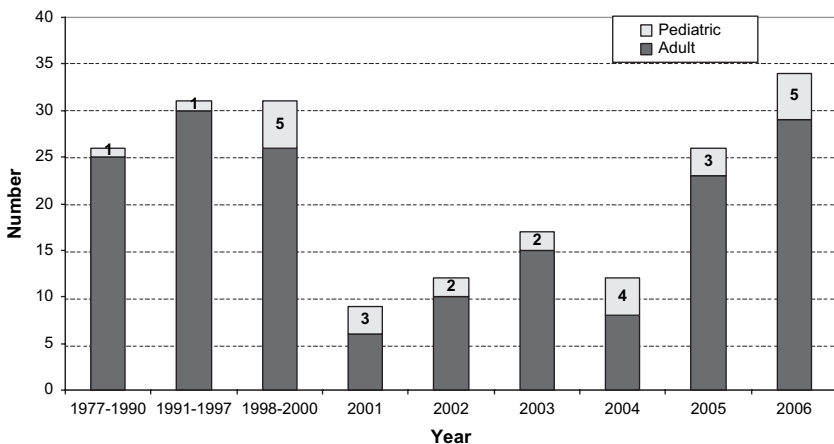


Fig. 3. Islet autograft experience at the University of Minnesota by era/year, including 198 patients (172 adults, 26 children younger than 18 years) from February 1977 to December 2006.

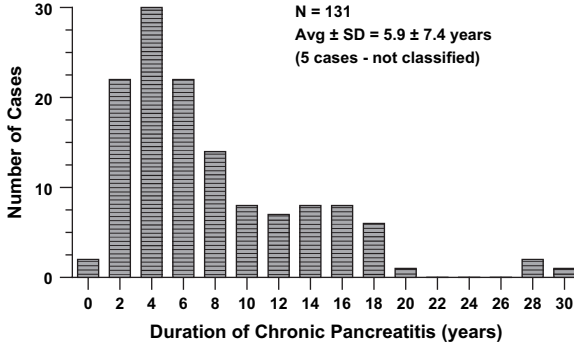


Fig. 4. Best estimated duration (in years) of chronic pancreatitis in 136 patients undergoing pancreatotomy and islet autotransplantation at the University of Minnesota from 1977 through 2004.

- Whipple—9
- Distal—12
- Combined (partial resection plus Puestow)—6

More than 75% underwent a TP or completion pancreatotomy at the time of their IAT (Box 2). This analysis [7] confirmed the correlation between the degree of pancreatic fibrosis and a prior Puestow procedure with attainment of low islet yields (Fig. 6). Again, we found a strong correlation between islet yield and insulin independence. Of patients receiving > 2000 IEQ/kg, 47% were completely insulin-independent while 25% required intermittent insulin.

From 2000 through 2005, the authors treated 43 TP patients whose metabolic status could be assessed relative to islet yield (Fig. 7). One third had

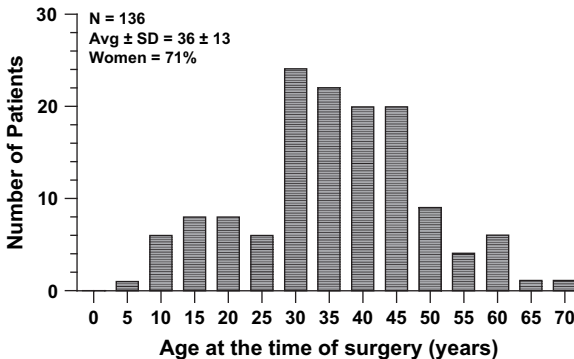


Fig. 5. Age and gender (71% female) distribution of 136 patients undergoing islet autotransplantation at the University of Minnesota from 1977 through 2004.

Box 1. Etiology of chronic pancreatitis in 136 patients undergoing pancreatectomy and islet autotransplantation at the University of Minnesota 1977 to 2004

Idiopathic—59 patients (43%)
 Alcohol—21 patients (15%)
 Divisum—17 patients (13%)
 Familial—15 patients (11%)
 Biliary—14 patients (10%)
 Iatrogenic—four patients (3%)
 Cystic fibrosis—three patients (1%)
 Trauma—two patients
 Congenital cyst—one patient

little or no islet function and were fully insulin-dependent. Another third had mild diabetes and needed insulin only intermittently or long-acting insulin once daily. The other third were insulin-independent. The mean islet yield was lowest in the completely insulin-dependent group and highest in the completely insulin-independent group, with the mean in the intermittent insulin group in between. There was much overlap between the groups, showing that factors other than simply the islet yield affect function and outcomes [7].

Cincinnati series

The most recent report from this group showed a 40% rate of insulin independence after TP/IAT, with a mean follow-up of 18 months [8,18]. Factors that correlated with postoperative insulin independence included the patient's weight, body mass index (BMI), and gender [37]. Patients who

Box 2. Operation performed in 136 patients undergoing pancreatectomy and islet autotransplantation at the University of Minnesota 1977 to 2004

- Complete pancreatectomy—105 (77%)
- Near total pancreatectomy—21 (15%)
- Distal pancreatectomy—10 (7%)
- Operating room time: 10 plus or minus 1.7 hours (2 to 4 hours waiting time for islet isolation)
- Estimated blood loss (EBL)—1500 cc (50 cc to 30 L)
- Length of stay (LOS)—22 days (1 to 89 days)



Fig. 6. Islet isolation yield by previous surgery in 136 patients undergoing pancreatectomy and islet autotransplantation at the University of Minnesota from 1977 through 2004.

had a BMI greater than 28 had a higher chance of insulin dependence [37]. Reduction to ideal body weight to minimize insulin resistance may maximize the chance for insulin independence after TP-IAT. Insulin-independent patients had lower mean insulin requirements during the first 24 hours after transplant, possibly relating to the detrimental effect of hyperglycemia on islet function [18]. Recent data involving 54 CP patients who underwent a TP-IAT showed that about two thirds had discontinued narcotics, and two-thirds had full or partial islet function, with about 40% insulin-independent [18].

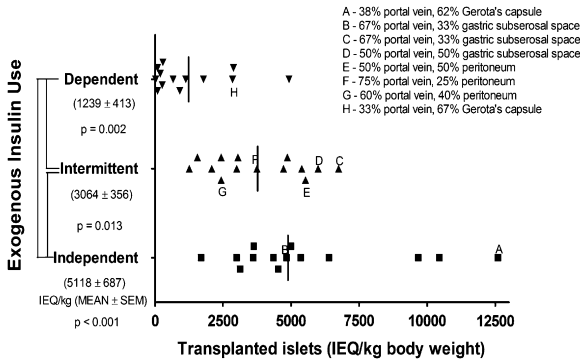


Fig. 7. Short-term metabolic outcome according to islet yield in 43 patients undergoing complete pancreatectomy and islet autotransplantation at the University of Minnesota from 2000 through 2004. The mean islet yield is higher in insulin-independent (versus -dependent) recipients, but there is considerable overlap.

Leicester series

The latest report from the Leicester series did not show any correlation between islet yield and insulin independence [43]. The results may relate to the cause of the CP (mostly alcohol) and possibly to patient compliance issues [43].

Comments

Insulin independence is only partially the goal of an IAT, because preserving any β -cell mass is beneficial. Indeed, islet allograft recipients who remain insulin dependent but have β -cell function and are C-peptide positive are metabolically more stable and less prone to hypoglycemic unawareness than those who have no β -cell function [97–99]. Furthermore, the risk of secondary complications is less in diabetics who receive or are C-peptide-positive [100–102]. By extrapolation, IAT recipients who are C-peptide positive, even with an insulin requirement, have a metabolic advantage. Although only one third of IAT recipients in the UMN series are insulin-independent long-term; another third have enough islets to achieve near normoglycemia with exogenous insulin, usually with one injection daily of the long-acting variety [7].

Although one third of the authors' IAT recipients become fully diabetic because of inadequate islet yield [7,32], as long as pain is relieved or improved, the operation is considered a success. The authors only offer IATs to patients who are fully informed about the risk of becoming diabetic, and who accept this risk in exchange for reasonable chances at both pain reduction and narcotic withdrawal. Some patients who became fully diabetic after TP-IAT because of inadequate islet yield, and who were particularly labile, have gone on to have a pancreas (allograft) transplant, and thus achieved insulin independence, but at the expense of needing immunosuppression [103]. An islet allograft also could be done in this situation, but an enteric-drained pancreas transplant is more attractive, because exocrine deficiency also can be corrected [34].

Long-term metabolic outcomes

One long-term study of metabolic outcomes in six TP-IAT recipients from the authors' center reported that diabetes mellitus was prevented for up to 13 (now 20) years (mean follow-up at study, 6.2 plus or minus 1.7 years) [33]. Normal fasting plasma glucose, intravenous glucose disappearance rate (κG), hemoglobin A_{1c}, insulin responses to intravenous glucose and arginine, and insulin secretory reserve were maintained, but insulin responses tended to decrease over time. The intravenous glucose disappearance rate correlated with the number of islets transplanted [33]. Another UMN study showed reduced functional β -cell secretory reserve in IAT recipients, as compared with healthy individuals [38]. A third UMN study showed

that intrahepatic islet grafts failed to secrete glucagon in response to sustained hypoglycemia, but did in response to arginine, a peculiarity that may be site-dependent [104]. Nonetheless, intraportal autografts of as few as 265,000 islets can result in release of insulin and glucagon, at appropriate times, and thus can result in prolonged insulin independence [105].

Quality of life and pain relief

Health-related QOL is significantly worse in patients who have CP, as compared with a gender- and age-adjusted general population [106]. The authors' primary goal in performing TP-IAT is to improve QOL by alleviating pain and giving patients a chance to discontinue narcotics, while preventing or minimizing surgical diabetes. Studies evaluating health-related QOL outcomes in this population are limited. In a report from Cincinnati, QOL as measured by a standard assessment tool (SF-36) showed significant improvement a mean follow-up of 19 months [37]. Prospective studies are needed.

In the Cincinnati series, unremitting abdominal pain refractory to high-dose narcotics was the indication for surgery in all TP-IAT patients [8,37]. Narcotic independence was achieved in 58% of the most recent 26 patients, with a marked reduction in narcotic use by pre- and postoperative morphine-equivalent determinations [8].

These findings are similar to those in the 1995 UMN series of 46 patients; in 83% of them, pain resolved or improved, and 81% were able to discontinue narcotics [28]. In the authors' recent review of 120 patients through 2004, 63% showed pain resolution or improvement [7]. Furthermore, a recent UMN analysis [107], based on an ongoing retrospective survey of TP-IAT patients, showed that nearly 95% of the adult patients reached stated they had less pain after the surgery. Nearly half were able to completely discontinue narcotics, and more than 95% stated they would recommend TP-IAT. The survey reached 75 adults (71% female, 29% male) at a median of 42 months after transplant.

In a recent small series from a group in Tennessee, 100% of patients who underwent TP for CP without IAT became narcotic-independent (median follow-up, 46 months) [108].

Narcotic independence may not be obtainable in patients with opioid-induced hyperalgesia (OIH). Such patients, after receiving narcotics for chronic pain, paradoxically become more sensitive to pain, by means of mechanisms originating in afferent neurons and in the spinal cord [109–114]. Future studies are needed to identify patients at risk of OIH and to develop effective strategies for narcotic discontinuation. OIH may be highly prevalent in patients referred for TP-IAT; accordingly, an endpoint such as narcotic independence may not be ideal for assessing postoperative success.

Cancer risk of chronic pancreatitis patients

The association between longstanding CP and cancer has been established [115–118]. It is believed that pancreatic cancer develops in the setting of CP, independent of the underlying etiology, but appears to require 30 to 40 years of inflammation before manifesting in an appreciable percentage of patients [116]. This increased risk for pancreatic cancer is potentiated by co-factors such as tobacco and likely by genetic factors that are not yet entirely identified [115,116].

A TP by itself for CP completely eliminates the risk of pancreatic cancer, but even with an IAT, the risk is lowered considerably, given the marked reduction in pancreatic tissue. The autologous islets infused into the portal system are never totally pure, but the use of tissue at risk for pancreatic cancer must be minimal. Sampling the whole gland for pathologic testing is impossible in the setting of an IAT. Patients who have hereditary and tropical pancreatitis are at higher risk for developing malignant cells than the rest of CP population [116,117], but again the amount of residual pancreatic tissue after TP-IAT is very small.

In the entire series of TP-IAT patients from UMN, no patients are known to have developed cancer in the liver or in any other site where the islets were auto-grafted, so the risk of cancer appears to be extremely low.

Future directions

A basic but important limitation to more widespread clinical application of IATs is the limited number of centers with the facilities and technology to isolate and prepare human islets. Few centers, including the authors', have used distance processing for both allogenic and autologous islets successfully [119–121]. The feasibility of distance processing is enhanced by new preservation methods that extend cold ischemic times and increase islet yield and viability from suboptimal organs [112–126].

The long-term success of IATs in patients who have CP [33] contrasts with the apparently less favorable long-term results for islet allotransplants in patients who have type 1 diabetes mellitus [98]. In the Edmonton islet allograft series, only 20% of recipients who became insulin-independent remained so at 5 years, although nearly all remained C-peptide-positive [98], indicating survival of β -cells. The difference in outcomes may be because of the rejection rate of islet allografts, or if allografts are not rejected, to the diabetogenic effect of the necessary immunosuppression.

Autologous islets are as fresh as possible. They are isolated from a pancreas that, although diseased, is not under the stress of brain death (which in animal models decreases islet yield and function by the activation of proinflammatory cytokines that occurs from central nervous system (CNS) injury [127]). A native pancreas removed for IAT also is not subjected to prolonged

ischemia or to hours of cold preservation that occur with deceased donor pancreases processed for allogenic islets.

Single-donor islet allografts have resulted in insulin independence in diabetic recipients at UMN [128]; yet in many cases, multiple donors are required [129]. Increasing islet viability for transplants is important; for allografts, one possibility is to use a living donor [27,130,131]. This approach should be effective, given the good outcomes in IAT recipients with an islet mass well below that required for a successful outcome with deceased donor islet allografts [132].

A secondary benefit of an IAT program is the opportunity to evaluate and compare differences in islet durability between islet autografts and allografts of the same β -cell mass. Such a comparison may allow one to make a distinction between immunologic and nonimmunologic factors that affect declines in, or sustenance of, islet graft function over time. Currently, however, it is apparent that IATs are more successful than their allogenic counterparts.

Summary

The main objective of this article was to show the benefit of IAT when combined with pancreatectomy to treat painful CP. IAT safely prevents or minimizes surgical diabetes after TP for benign disease. Pancreatic resection (even partial) with an IAT always should be considered the primary surgical option for patients who have CP and intractable pain refractory to medical or endoscopic therapy. Pain relief, enabling narcotic discontinuation, is the primary objective; the prevention of diabetes is a secondary goal. The series reviewed here, extending back 30 years, shows that both goals are achieved to a reasonable degree in a very difficult disease, CP.

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