Journal on Surgery
www.journalonsurgery.org

Review Article

ISSN: 2691-7785

Open Access, Volume 4

Pancreas Transplantation for the Treatment of Pancreatic Exocrine Disorders

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Abstract

Pancreas transplantation is mostly performed to cure diabetes mellitus. However, patients with chronic pancreatitis, cystic fibrosis, benign pancreatic tumors or patients with other exocrine disorders of the pancreas can also be candidates for a pancreas transplant in combination with a kidney, liver or lung or for a pancreas transplant alone. With improvement in surgical techniques and immunosuppressive therapy, pancreas transplant outcomes have improved significantly over the past decade.

Mounting evidence supports pancreas transplantation for the treatment of exocrine disorders as an important therapeutic option to restore both endocrine and exocrine function of the pancreas. Patient and graft survival rates are similar to those for pancreas transplants in diabetic patients. A successful pancreas transplant is also more cost efficient and puts less burden on health care spending. However, the risk of immunosuppression and surgery should be carefully evaluated and discussed with the patient. In this review article, we discuss pancreas transplantation for pancreatic exocrine disorders: indications, other treatment options, and outcomes.

Keywords: Pancreas transplantation; Diseases of the Pancreas; Exocrine deficiency; Chronic Pancreatitis; Benign pancreatic malignancy; Cystic Fibrosis; Pancreas auto transplantation; TPIAT.

Introduction

Pancreas transplantation is unique from other solid organ transplants such as the liver, kidney, heart or lung because the entire organ is usually not needed for the purpose of transplantation. This 100 gram organ consists of two types of tissues with different functions: exocrine and endocrine. Ninety-eight percent of the pancreas volume is exocrine tissue and only one or two percent is endocrine tissue. The vast majority of pancreas transplants is performed to replace the endocrine function of the pancreas in diabetic patients. However, for less common indications, a pancreas transplant may be performed to restore both the exocrine and the endocrine function of the pancreas [1].

Pancreas transplant options include: (1) segmental pancreas autotransplants or islet autotransplant in patients with chronic pancreatitis; (2) pancreas allotransplants for selected patients with a previous native pancreatectomy to treat chronic pancreatitis; (3) pancreas autotransplant in selected patients with malignancy; and (4) pancreas or islet allotransplants (as part of "cluster" transplants) in selected patients to treat upper-abdominal malignancies.

Chronic pancreatitis

Chronic pancreatitis is a progressive fibro-inflammatory disease that causes the destruction of pancreatic exocrine and en-

Manuscript Information: *Received: Mar 12, 2024; Accepted: Apr 12, 2024; Published: Apr 19, 2024*

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Citation: *Gruessner RWG, Laftavi MR, Pankewycz O, Gruessner AC. Pancreas Transplantation for the Treatment of Pancreatic Exocrine Disorders. J Surgery. 2024; 4(1): 1158.*

docrine tissue. Eventually, the secretory parenchyma is replaced with fibrotic tissue. Chronic pancreatitis comprises a number of etiologies and classifications. According to one classification, three types can be distinguished: Chronic calcifying pancreatitis, chronic obstructive pancreatitis, and steroid-responsive pancreatitis (chronic autoimmune).

Genetic, metabolic, environmental, toxic and/or other risk factors can lead to persistent pathologic changes of the pancreas including severe parenchymal injury [2]. Advanced stages of chronic pancreatitis may include histopathological changes such as pancreatic atrophy, fibrosis, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, dysplasia; once diagnosed, these changes are irreversible [1]. The most distressing feature of chronic pancreatitis and recurrent episodes of acute pancreatitis is intractable pain, resulting in opioid addiction, extremely poor quality of life and disability, all of which are usually worse than those seen in other common chronic disorders and cancer [3-5]. The progressive inflammatory acinar process eventually impacts the beta cells as well and may cause brittle diabetes mellitus [6-8].

Chronic calcifying pancreatitis is the most common type of chronic pancreatitis. It causes development of stones in the main pancreatic duct and/or in the side branches and may result in pancreatic duct distortion, stricture, and pancreatic atrophy. In contrast, obstructive or autoimmune chronic pancreatitis rarely cause calcifications of the pancreas.

Chronic obstructive pancreatitis usually results from primary injury to the duct or from partial or complete ductal obstruction [9-11]. Obstructive pancreatitis occurs upstream from a pancreatic duct stricture. It is caused by pancreatic duct injury for a variety of reasons including endoscopic or surgical procedures, acute necrotizing pancreatitis, blunt abdominal trauma, narrowed pancreatico-enteric anastomoses and tumors obstructing the pancreatic duct (eg, ductal adenocarcinoma or intraductal papillary mucinous tumor). Ductal obstruction due to strictures and stones can also cause chronic calcifying pancreatitis. In the typical form of chronic obstructive pancreatitis, only the organ upstream from the obstruction is affected, with the downstream pancreas being healthy and of normal appearance.

Steroid-responsive or autoimmune chronic pancreatitis is a type of chronic pancreatitis that responds well to corticosteroid therapy. Autoimmune pancreatitis is categorized in two types: type 1 and type 2. They are different entities. Type 1 is generally associated with true autoimmune pancreatitis and it has been suggested to call this form autoimmune pancreatitis whereas type 2 should be called idiopathic duct-centric chronic pancreatitis [12].

Type 1 steroid-responsive chronic pancreatitis is the pancreatic manifestation of a multiorgan fibro-inflammatory syndrome known as immunoglobulin G4-related syndrome. This syndrome presents with multiorgan involvement, characteristic histology, an increase in serum IgG4 levels, and a rapid response to corticosteroid. The IgG-4 related disease manifests itself in several organs such as the pancreas, bile ducts, salivary glands, retroperitoneum, kidneys, and lymph nodes [13]. The histopathology shows dense lymphoplasmacytic infiltrates around the mid-size ducts, a peculiar swirling (storiform) fibrosis, an intense inflammation that surrounds the veins and spares adjacent arteries, and frequent IgG4 plasma cells. The most common symptom of type 1 autoimmune pancreatitis is obstructive jaundice. Less often, it presents with acute pancreatitis. Pain is not severe nor as common as with other types of chronic pancreatitis and resolves rapidly with corticosteroid therapy. Calcification is not frequently observed and may occur after multiple relapses of the disease [14].

Idiopathic duct-centric chronic pancreatitis (type 2) differs substantially from type 1 autoimmune chronic pancreatitis. Histopathology of this type shows a picture in which the pancreatic duct epithelium is infiltrated by neutrophils. Type 2 chronic pancreatitis inclines to cause multiple recurrent bouts of acute pancreatitis.

According to the Pancreas Foundation pancreasfoundation.org [15], the annual incidence rate of chronic pancreatitis is 5-12/100,000 people in industrialized nations. The prevalence of chronic pancreatitis is 50/100,000 people. Chronic pancreatitis often develops in patients between the ages of 30 and 40, and is more common in men than women.

Factors that increase the risk of chronic pancreatitis are alcohol, smoking, autoimmune and anatomical abnormalities, but genetic factors were also well recognized. Genetic variations associated with chronic pancreatitis are PRSS1 (Protease, Serine 1, a cationic trypsinogen), SPINK 1 (serine protease inhibitor kazal-type 1), and CFTR (cystic fibrosis transmembrane conductance regulator) and, to a lesser degree, CTRC (chymotrypsin C) and CASR (calcium-sensing receptor) [16]. The polymorphism and mutation have several mechanisms and variations. The most recognized gene associated with chronic pancreatitis is PRSS 1. More than 40 mutations in the *PRSS1* gene have been found to cause hereditary pancreatitis and most of these mutations change single protein building blocks (amino acids in cationic trypsinogen). Some *PRSS1* gene mutations result in the production of a cationic trypsinogen enzyme that is prematurely converted to trypsin while it is still in the pancreas. Other mutations prevent trypsin from being broken down. The most common *PRSS1* gene mutation that causes hereditary pancreatitis replaces the amino acid arginine with the amino acid histidine at position 122 in the enzyme (written Arg122His or R122H). As a result of this mutation, the enzyme cannot be broken down, even when it is no longer bound to calcium. Genetic chronic pancreatitis has a different course than other forms of chronic pancreatitis. It is associated with early onset, rapid progression to chronic pancreatitis and a high risk of pancreatic adenocarcinoma. Genetic testing may be considered in patients with pancreatitis at age below 25 who have had recurrent episodes of acute pancreatitis with an idiopathic etiology [17].

Medical therapy for chronic pancreatitis

Lifestyle modifications, cessation of alcohol use and smoking, exercise, avoiding weight gain and a multidisciplinary approach by a dedicated chronic pancreatitis team including surgeon, gastroenterologist, dietician, social worker, psychologist, pain management specialist and pharmacist are essential in the management of this complicated chronic disease.

The medical treatment of chronic pancreatitis can be categorized according to treatment of (1) pain, (2) exocrine and endocrine deficiency, and (3) complications of chronic pancreatitis such as bleeding, obstruction and cancer.

Severe abdominal pain is the major complaint and it is experienced in 50-85% of patients. Management of abdominal pain is challenging and has a high rate of failure [18]. Ceyhan et al. [19] showed that pancreatic sympathetic innervation was significantly reduced in chronic pancreatitis and pancreatic cancer, whereas parasympathetic innervation did not show major changes. Nestin neuro-immunoreactivity was stronger, and Sox10-immunoreactivity was weaker in chronic pancreatitis and pancreatic cancer than in normal pancreata. Pancreatic sympathetic and cholinergic innervation was noticeably decreased in patients with severe pancreatic neuritis, neural invasion by cancer cells, or abdominal pain. Moreover, the neural immunoreactivity for Nestin and Sox10 also varied with intrapancreatic neuropathic alterations and abdominal pain. Other studies showed that in chronic pancreatitis, intrapancreatic nerves are remarkably enlarged and increased in number and the structure of the intra-pancreatic nerves was altered [20,21]. Nerves are frequently surrounded by inflammatory cells that often infiltrate these nerves through a damaged perineurium and cause the characteristic pancreatic neuritis [22]. The important role of these neural and perineural alterations in the pathogenesis of pain in chronic pancreatitis was already suggested in the mid-1980s. More recent studies have shown a positive correlation between these neuromorphological changes in chronic pancreatitis and the degree of pain experienced by patients [23,24].

Several treatment options have been suggested to manage abdominal pain in patients with chronic pancreatitis. Opioids can lead to tolerance and dependence and should be carefully assessed before utilization. Tricyclic antidepressants, selective serotonin-reuptake inhibitors, gabapentin, and pregabalin have been used either alone or in combination with opioids with different outcomes. Winstead and Wilcox [25] reviewed the literature regarding the use of pancreatic enzymes in the treatment of chronic pancreatitis pain. They recommended that the pain should be assessed in a standardized and repeatable fashion prior to initiating a therapeutic trial of pancreatic enzymes. Therapeutic trials should be limited to 6 weeks with uncoated enzymes and concurrent acid suppression, at which point another standardized pain measurement questionnaire should be completed. They also suggested that one group of patients is not more likely to benefit from this intervention than another; however, it may be more effective for women with nonalcoholic chronic pancreatitis. Since only this one report regarding uncoated enzyme therapy showed significant improvement in pancreatic pain management, they did not recommend routine use of pancreatic enzymes in the treatment of painful chronic pancreatitis.

A double-blinded, randomized, controlled trial, the ANTICIPATE study [26], reported in 70 patients at 6 months a reduction of pain scores by 1.97 from baseline in the placebo group and by 2.33 in the antioxidant group, but there was no statistically significant difference between the groups (-0.36; 95% Confidence Interval [CI], -1.44 to 0.72; *P*=.509). The average daily pain scores from diaries were also similar (3.05 for the placebo group and 2.93 for the antioxidant group, a difference of p=0.11; 95% CI, 1.05-0.82; *P*=.808). Measures of quality of life were similar between groups, as was opiate use and number of hospital admissions and outpatient visits. Blood levels of vitamin C and E, β-carotene, and selenium were increased significantly in the antioxidant group. However, the use of antioxidants did not reduce the pain or improve quality of life, despite increase of the antioxidant in the blood.

Thoracoscopic splanchnicectomy was first described as minimally invasive therapy for pain in chronic pancreatitis in 1994 [27]. With this procedure, the nociceptive input of the pancreas is interrupted by denervating the splanchnic nerves at the level of the thorax before they enter the sympathetic cord. Some studies showed relief of pain by this procedure for short-term [28,29]. However, the long-term outcome did not reveal a significant reduction of the chronic pancreatic pain. New evidence suggests that the failure of this procedure results from prolonged use of opioids that sensitizes the peripheral nerve, leading to permanent hyperalgesia that is difficult to cure and reverse [30-32].

Surgical interventions for chronic pancreatitis

Non-transplant surgical options

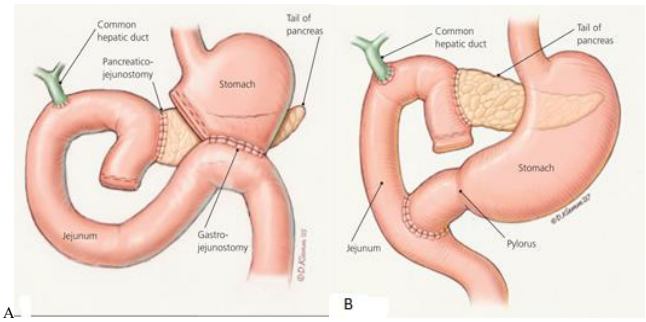
A good number of patients with chronic pancreatitis may not respond to multiple medical therapies [33]. Surgical interventions may be useful in selected patients. Different surgical interventions are recommended for patients with poorly controlled abdominal pain, duodenal, biliary or pancreatic obstruction, symptomatic pseudocyst, or suspicion of cancer. The surgical interventions that are commonly used can be classified into 4 categories: (1) drainage procedures, (2) partial pancreatic resection, (3) a combination thereof and (4) total pancreatectomy with or without islet autotransplantation.

The techniques for drainage procedures have evolved over time. Du Val and Zollinger et al. almost simultaneously described retrograde pancreatic duct drainage into a defunctionalized jejunal loop. This procedure includes resection of both a (small) portion of the pancreatic tail and spleen [34,35]. Puestow et al. described caudal pancreaticojejunostomy to drain multiple strictures and dilatations (a so-called “chain of lakes”) frequently associated with chronic pancreatitis: the pancreatic duct is opened longitudinally from the transected tail to a point just to the right of the superior mesenteric vessels; this portion of the pancreas is anastomosed to the end of a jejunal Roux-en-Y loop [36]. Partington and Rochelle described a side-to-side pancreaticojejunostomy with the pancreatic duct opened all the way from the pancreatic tail to its entry into the duodenum; resection of any portion of the pancreatic tail or spleen is not required [37].

Drainage procedures may be combined, not only with resection of a small portion of the tail of the pancreas (as described by Du Val, Zollinger et al., and Puestow et al.), but also with (partial) resection of the pancreatic head. Indeed, the head of the pancreas has been coined “the pacemaker” of chronic pancreatitis. Up to 35% of patients develop an inflammatory mass with an enlarged pancreatic head. The combination of a drainage procedure and resection of the anterior portion of the pancreatic head was described by Frey and Smith [38]. Coring out the pancreatic head and the uncinate process not only removes diseased tissue but also allows drainage of Wirsung’s duct, Santorini’s duct, the duct to the uncinate process, and their tributary ducts. The unroofed pancreatic ducts and the partially resected pancreatic head with the uncinate process are drained side-to-side using a jejunal Roux-en-Y loop.

Resective procedures can be classified into two groups: (1) partial resection of the pancreas (e.g., standard Whipple procedure,

pylorus- or duodenum-preserving resection of the pancreatic head, distal pancreatectomy) (Figures 1 and 2) complete resection of the pancreas (with or without preservation of the pylorus or duodenum). Advantages of partial resection are that (1) almost half of the pancreatic tissue is left behind and (2) patients may not develop exocrine or endocrine deficiency. However, the incidence of endocrine insufficiency after partial resection increases with time.



Whipple procedure without pylorus preservation (A) and with pylorus preservation (B).

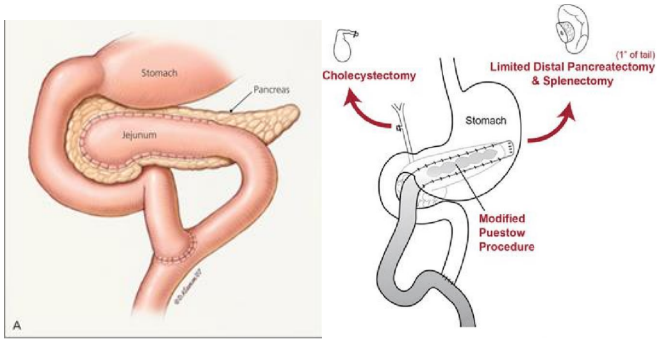


Figure 1: Top: Whipple procedure without pylorus preservation **(A)** and with pylorus preservation **(B)**. Bottom: Modified puestow procedure with distal pancreatectomy and splenectomy.
Cited from Journal of Pancreatic Cancer 4(1): 60-63.

The standard Whipple procedure [39] or the duodenum-preserving resection of the pancreatic head (to Beger et al. [40] is performed if chronic pancreatitis is predominantly located in the pancreatic head (frequently associated with an enlarged, inflammatory mass) and if the tail of the pancreas shows little evidence of chronic pancreatitis. The advantage of a duodenum-preserving resection is that it excludes surgery of the stomach, duodenum, and biliary tree, but it requires creation of two pancreatic anastomoses (one to the distal pancreas and one to the remnant of the pancreatic head). In contrast, the standard Whipple procedure (with or without pylorus preservation) removes the whole pancreatic head, involves surgery of the biliary tree, and is associated with a higher rate of endocrine insufficiency.

Distal pancreatectomy is indicated for patients whose disease process is mainly confined to the distal pancreas. Its morbidity and mortality are lower than for resective procedures of the head, and it only infrequently exacerbates exocrine or endocrine insufficiency. However, radical distal pancreatectomy (85% to 90% resection) carries a much higher risk of exocrine or endocrine insufficiency than standard distal pancreatectomy (40% to 60% resection). Distal pancreatectomy for chronic pancreatitis can be done with or without spleen preservation. Of note, about 20% to 40% of patients with partial or complete resection of the pancreatic head show, on further imaging, progressive changes of chronic pancreatitis in the pancreatic body and tail within 6 to 12 months after the initial resection. Such patients often experience recurrent pain and may require a completion distal pancreatectomy. Vice versa, if, after distal pancreatectomy, subsequent imaging of the pancreatic head shows evidence of progressive pancreatitis and if severe pain recurs, then a completion proximal pancreatectomy may be indicated. In addition, diabetes is estimated to develop long-term in 80% of patients who undergo near-total (i.e., 80% to 95%) distal resection.

Total pancreatectomy remains the surgeon's last resort in the treatment of chronic pancreatitis. This procedure inevitably results in complete exocrine and endocrine insufficiency of the pancreas. A "radical" therapy for a "benign" disease, it is still associated with a high morbidity and mortality rate. In addition, up to one third of patients do not achieve pain relief and continue to require opiate-driven analgesia [8-11]. Total pancreatectomy is usually performed only after all other treatment modalities (including the resective procedures above) have failed. Three techniques for complete removal of the pancreas have been described: (1) duodenum-preserving total pancreatectomy, which involves dissection of the distal bile duct away from the pancreas and resection of the pancreatic tissue, by sharp dissection, between the bile duct and the first and second parts of the duodenum; (2) pylorus-preserving total pancreatectomy in which jejunum is brought up from the ligament of Treitz and anastomosed end-to-end with the first portion of the duodenum, and an end-to-side choledochojejunostomy is created 10 cm distally; and (3) total pancreatectomy, without preservation of the duodenum or pylorus [41-44].

After total pancreatectomy, treatment of exocrine insufficiency is usually considered easier than treatment of the ensuing surgical diabetes mellitus. Patients frequently develop a brittle form of diabetes mellitus: they are particularly sensitive to insulin and prone to hypoglycemic episodes because of the lack of other glucose regulatory hormones such as glucagon. As a consequence, they show wide oscillations between hypo- and hyperglycemia. Hospitalizations because of hypoglycemia, ketoacidosis, and failure to thrive are not uncommon. In fact, hypoglycemic unawareness is a well-described cause of death after total pancreatectomy [45,46].

A good number of patients suffering from chronic pancreatitis continue to be devastated by the pain and poor quality of life despite much surgical and medical therapy [47-50].

Drainage procedures usually provide good long-term pain relief in only 10% to 30% of patients and partial or complete resection of the pancreas in 20% to 50%.

Total Pancreatectomy with Islet Auto-Transplant (TPIAT)

Pain relief is the primary objective of surgery for chronic pancreatitis. An additional objective of pancreas or islet autotransplant, alternatives to the classic drainage and resective procedures, is to prevent severe endocrine deficiency. Patients scheduled to undergo total or near-total pancreatectomy might as well undergo a simultaneous pancreas or islet auto-transplant, which, in addition, offers the chance of being insulin independent or at least makes their diabetes easier to manage. But, surprisingly, despite the success of simultaneous pancreas or islet autotransplant, they are still not mentioned in many standard textbooks of surgery.

Moran et al. studied 46 patients who underwent total pancreatectomy and autoislet transplant. They showed that, following surgery, 89% of patients had resolution of their pre-operative abdominal pain; however, 83% of patients developed a different form of abdominal pain. Opioid independence was achieved in 46% of patients. Acute recurrent pancreatitis (OR: 11.66; 95% CI: 1.47-92.39; p=0.02) but not pain duration >3 years or ≥ 5 ERCPs was independently associated with resolution of pre-operative abdominal pain on multiple logistic regression. None of these factors were associated with cessation of opioid use [51].

After total pancreatectomy, patients will develop type 3c brittle diabetes with widely-fluctuating blood sugar levels that are very difficult to control due to removal of both insulin and glucagon secreting cells [52]. For this reason, islet-auto transplant is offered to these patients to restore euglycemia [53-55]. However, some patients with chronic pancreatitis already suffer from diabetes due to inflammatory and fibrosis damage to islet cells and therefore, islet auto-transplant is not feasible. Furthermore, in many patients, an optimal islet cell yield cannot be obtained for auto-transplantation due to the severely damaged endocrine cells caused by chronic pancreatitis.

Adams et. al. [56] reported that of 160 patients with total pancreatectomy and islet auto-transplant, 73(48.8%) developed significant side effects including delayed gastric emptying in 20(12.5%) patients, pneumonia in 23(14.4%), intraabdominal abscesses in 10(6.25%), unplanned reintubation in 9(5.6%), acute renal failure in 8(5.0%), septic shock in 6(3.8%) and wound infection in 6(3.8%). Post-operative hospital length of stay was 12.4±1.0 days, reoperation was required in 17 patients (10.6%) and readmission in 46 patients (28.8%). Thirty-day mortality was observed in 2 patients (1.25%) and 90-day mortality in 4 patients (2.5%.) One hundred and sixty patients were available for long-term follow-up, of whom 13 patients died (8.1%). The median duration of follow-up was 4.8±0.2 years. They concluded that total pancreatectomy with islet auto-transplant has its own significant side effects.

In another study by Al-sofiani et al, only one-third of their patients achieved insulin independence and up to 75% required insulin therapy after islet auto- transplant [57].

Total pancreatectomy and islet auto-transplant does not cure exocrine insufficiency. Thus, the most biological therapy to replace the removed pancreas is pancreas transplantation to restore both endocrine and exocrine function of the pancreas. The disadvantage of this therapy is surgery and immunosuppression. Pancreas transplant surgery has evolved over time due to many advances in surgical techniques [58] and surgical complications resulting in pancreas graft loss have declined to less than 10% at the majority of transplant centers. Furthermore, the rate of graft loss from rejection has also significantly declined to 3% in SPK and 8% in PAK and 15% in PTA recipients [59].

Pancreas allotransplantation after total pancreatectomy for chronic pancreatitis

Most pancreas transplants are performed to cure diabetes; only 0.1% of pancreas transplants have been performed after total pancreatectomy in the US (Table 1).

Table 1: Pancreas transplant primary diagnosis, USA data (1994-2020). Courtesy of Dr. Angelika Gruessner (IPTR), January 2021.

Diagnosis	PAK	PTA	SPK	Total
Diabetes secondary to chronic pancreatitis without pancreatectomy	1	4	9	14
Diabetes secondary to cystic fibrosis without pancreatectomy	2	1	3	6
Pancreatic cancer	0	2	2	2
Bile duct cancer	1	1	2	4
Other cancer	0	0	4	4
Pancreatectomy prior to pancreas transplant	1	41	10	52
Diabetes mellitus- unknown etiology	1	0	30	31

PAK: Pancreas after Kidney Transplant; PTA: Pancreas Transplant Alone; SPK: Simultaneous Pancreas and Kidney Transplant.

The first pancreas transplant after total pancreatectomy was reported in 1991 by Dr. Gruessner from the University of Minnesota [60].

In 2008, Gruessner et al. reported a series of 26 patients who underwent a total pancreatectomy and a subsequent pancreas allotransplant. In his report, patient survival rates at 1- and 3-years in both the CSA and TAC eras were 100% and 100%; in the CNI-free era, at 1 year, the survival rate was lower due to the small number of transplants. Pancreas graft survival rates in the CSA era were 67% and 50% at 1 and 3 years, respectively; in the TAC era, 73% and 51%, respectively; and in the CNI-free era, at 1 year, 40% (p=0.13). The mean number of rejection episodes in the CSA era was 2.1; in the TAC era, 1.4; and in the CNI-free era, 0.6. It was concluded that (1) pancreas allotransplants in patients with a previous total pancreatectomy for chronic pancreatitis can achieve pancreas graft survival rates of 70% with TAC-based immunosuppression; (2) pancreas transplants can successfully treat both endocrine and exocrine insufficiency; and (3) sequential pancreas allotransplants should be considered a treatment option in patients with pancreatectomy-induced brittle diabetes mellitus or with progression of secondary complications of diabetes mellitus [61].

In a European study [62], eight patients (1.4% of total pancreas transplants) underwent pancreas transplant alone after total pancreatectomy due to chronic pancreatitis. Patient and graft survival rates were 88% and 88% at 1-year and 88% and 75% at 3-years, respectively. One patient died due to sepsis caused by vancomycin-resident bacteremia and subsequent graft-versus-host disease almost one year after the transplant. Median hospital stay, rejection and infection rates were not different than for pancreas transplants without prior pancreatectomy. Seventy-five percent of the patients remained insulin-free for up to 5-years. Seventy-five percent of patients with documented pancreatic enzyme supplement use pre-transplant did not need further pancreatic enzyme supplementation post-transplant. Thirty-three percent of patients could be weaned off from narcotic medications for pain control.

Cystic fibrosis

According to the International Pancreas Transplant Registry (IPTR), 26 transplants including the pancreas were performed for cystic fibrosis in the U.S. between January 1988 and December

2020 (Table 2). There were 6 transplants in the traditional pancreas transplant categories (SPK 3, PAK 2, PTA 1) and 20 various multiorgan transplants including the pancreas. Of the 20 pancreas-multiorgan transplants, only 1 (a combined pancreas-intestine transplant) did not include the liver.

Table 2: Pancreas transplants for cystic fibrosis, USA data (1988-2020).

Transplant type	Frequency
PAK	2
PTA	1
SPK	3
Liver Intestine Pancreas	2
Liver Kidney Pancreas	1
Liver Pancreas	14
Liver Pancreas Lung	2
Pancreas Intestine	1

PAK: Pancreas after Kidney Transplant; PTA: Pancreas Transplant Alone; SPK: Simultaneous Pancreas and Kidney Transplant. There were 6 transplants in the traditional pancreas transplant categories and 20 various multiorgan transplants including the pancreas.
Courtesy of Dr. Angelika Gruessner (IPTR), June 2021.

Usatin et al. [62] reviewed United Network for Organ Sharing (UNOS) data from 1987-2014, and reported that of 4,600 patients with cystic fibrosis, 17 patients underwent liver-pancreas, 4 patients pancreas-kidney, 3 patients pancreas-lung, 3 patients pancreas only, and 1 patient liver-lung transplants. Two-years graft survival rates were 88% for liver-pancreas, 33% for lung-pancreas and 100% for pancreas-kidney and pancreas alone transplants. It was concluded that despite ninety percent of patients with cystic fibrosis suffering from pancreatic exocrine insufficiency and 26% developing diabetes after 10 years of the disease, pancreas transplant is still underutilized in these patients.

Other than chronic pancreatitis and cystic fibrosis, pancreas transplants are performed in patients with benign pancreatic tumors such as intraductal papillary mucinous neoplasia (see below) [63]. There have been concerns regarding the use of immunosuppressive drugs in patients with a history of cancer. However, currently, solid organ transplants are offered to patients after being cancer-free for a certain period of time [64,65] or patients with hepatocellular carcinoma [66-69] or colorectal cancer under certain conditions [70,71]. One European study [63] showed that when patients who had been cancer-free for a certain period of time were accepted for pancreas transplantation, an increase of 15 pancreas transplants per year was noted in their program.

Cost effectiveness of pancreas allotransplantation for exocrine disorder

The cumulative cost of insulin for 20 years is estimated to be about $663,000 per patient and 9.3 quality-adjusted life years. The average cost-effectiveness ratio being $71,000 per quality-adjusted life years. The cumulative cost for islet allotransplantation is estimated to be nadir of $519,000 and a cumulative effectiveness of 10.9 quality-adjusted life years [72]. Vrochides et al. [73] showed that the cumulative cost for whole pancreas transplant is about $40,000. In 2014, a study from United Kingdom reported 12,000 admissions per year due to chronic pancreatitis. Estimated cost was £55.8 million per year. This is equal to £71,000 (or $113,000) per patient per year [74]. Other reports [75-77] also confirm the cost effectiveness of pancreas transplantation compared to other treatment options for chronic pancreatitis.

Historical overview of now obsolete pancreas auto- and allotransplants

For reasons of completeness, a history of now obsolete pancreas auto- and allotransplants is provided here as well [78].

Pancreas autotransplants for chronic pancreatitis

Pancreas autotransplants were basically performed at a time when the islet isolation process in many ways was still in its infancy and islet cell yields were poor.

The concept of heterotopic autotransplantation of the segmental pancreas to treat chronic pancreatitis was introduced by Hogle and Reemtsma in 1978 [79]. They described two cases in which the segmental autografts were anastomosed with their splenic vessels to the femoral vessels; the pancreatic ducts were ligated, with one patient requiring drainage of a groin abscess. Of the two patients, one had a functioning graft 3 years post-transplant; the second was lost to follow-up. Tosarti et al. described three patients with chronic pancreatitis who underwent segmental autotransplants with vascular anastomosis also to the femoral vessels: The pancreatic ducts were injected with 8 mL of neoprene, but all three patients developed pancreatic fistulas [80]. At 12 to 16 months posttransplant, all three patients were free of pain and insulin independent.

Rossi et al. described 10 patients with chronic pancreatitis who underwent heterotopic segmental pancreatic autotransplants after near-total (95%) pancreatectomy: A small rim of pancreatic tissue was left attached to the duodenum to preserve the integrity of the common bile duct and part of the duodenal blood supply [81]. The pancreatic body and tail (50% to 60% of the gland) were prepared for autotransplantation; the pancreatic duct was injected with 1.5 to 2.5 mL of neoprene and ligated. The remainder of the resected pancreas was submitted for histopathologic studies. The splenic vessels were anastomosed end to side to the common femoral vessels, and the segmental autograft was placed in a subcutaneous pocket overlying the vastus lateralis muscle [81,82]. To reduce the risk of venous thrombosis, an arteriovenous fistula between the distal splenic artery and vein was constructed in patients with small pancreas grafts. The initial bulge from the graft progressively decreased and disappeared in 3 to 4 months. With a median follow-up of 31 (range, 24 to 54) months, Rossi et al. reported that heterotopic pancreas autotransplants were technically successful in 8 of these 10 patients. Only one of them required insulin at 2 years post-transplant; the other seven patients with technically successful grafts had remained insulin independent.

Pancreas autotransplants provide an opportunity to assess the long-term function of segmental grafts without the influence of rejection and the effects of immunosuppression. In some series, patients with near-total or staged-total pancreatectomy showed decreased insulin responses after pancreas auto transplants [81,82]. But, the loss of endocrine function as a result of ductal occlusion occurred more slowly in humans than in large animals

[83,84]. Hyperinsulinemia as a result of systemic vein drainage has been documented after pancreas autotransplants. Rossi et al. also found that patients with "idiopathic" chronic pancreatitis appeared to have better pain relief and better preservation of endocrine function, as compared with alcoholic patients with chronic pancreatitis [82]. They also discussed the rationale for pancreas (vs islet) auto transplants at the time. The combination of decreased islet cell mass, the low yield of then-current methods of islet cell isolation, and the limited results reported with intraportal islet auto trans-plants for chronic pancreatitis had dissuaded them from using islet auto transplants [82].

Subsequently, several modifications for heterotopic pancreas auto transplants were reported: Use of the pancreatic body only, with anastomosis of the proximal splenic vessels to the common femoral vessels and ligation of both ends of the pancreatic duct [85]; staged enteric drainage with a Roux-en-Y anastomosis to the pancreatic duct [86]; extra peritoneal anastomosis of the splenic vessels to the iliac vessels, with primary enteric drainage of the pancreatic duct to a Roux-en-Y loop, with or without temporary placement of a percutaneous stent in the pancreatic duct [87]; and extra peritoneal placement and anastomosis of the splenic vessels to the iliac vessels with pancreaticocystostomy [88].

Auto transplants into the iliac fossa (with anastomosis to the iliac vessels) appeared to be less prone to surgical complications than autotransplants into the groin (with anastomosis to the common femoral vessels). Groin complications, such as transient or permanent pancreatic fistulas, pancreatitis, and hematomas or bleeding from the femoral muscles, usually resulted in lower quality of life, as compared with complications that arose from the iliac fossa. As with segmental allotransplants, intraperitoneal placement of segmental autotransplants appeared to cause the lowest complication rate and so might be the best way to decrease posttransplant complications.

The surgical techniques for managing exocrine pancreatic secretions developed in a similar fashion for segmental autotransplants as they did for segmental allotransplants: from duct ligation and duct injection to enteric or bladder drainage. Although improvements in exocrine function cannot be expected by enteric drainage in patients with chronic pancreatitis, enteric drainage may be the choice to preserve the existing level of exocrine function [85].

Removal of remaining ductal calculi and debris was desirable but often not technically feasible. Yet, reestablishment of pancreatic duct patency may have prevented further progression of fibrosis: Long-term evaluation of the exocrine pancreas function (as assessed by the exocrine pancreas function diagnostic test, expressed as the urinary excretion rate of orally administered p-aminobenzoic acid) showed that posttransplant values were either similar to or slightly higher than pretransplant values [87]. For those reasons, enteric drainage was considered the choice for segmental autotransplants: Open duct drainage inevitably caused pancreatic fistulas; duct ligation and duct occlusion may have promoted progressive fibrosis of the pancreas graft, as in large animals [83,84,89]; and bladder drainage may have required bicarbonate supplementation in patients with remaining exocrine function.

Preservation and storage of segmental autografts should be identical to those of segmental allografts from living or deceased donors: Autografts should be flushed with small amounts (20 to 50 mL) of University of Wisconsin (UW) solution via the splenic artery and, until implantation, stored in UW solution. To reduce ischemia times of up to 300 minutes [84], the iliac vessels at the implantation site should be dissected out before the splenic vessels of the native pancreas are ligated and divided. Decreased ischemia time may benefit the remaining endocrine as well as exocrine function of the segmental autograft.

Because of denervation of the autograft, autotransplants did not appear to create the typical pain syndrome associated with chronic pancreatitis. Although isolated occurrence of groin pain and pancreatitis had been reported [81], it was most likely related to the duct occlusion technique rather than to the underlying disease.

The primary aim of segmental pancreas autotransplants at the time of insufficient islet processing was to preserve islet function and prevent or delay the onset of diabetes mellitus. Short- and long-term studies in recipients who were not insulin dependent before their autotransplants showed that both oral and Intravenous Glucose Tolerance Tests (IVGTTs) in most remain similar to, somewhat better than [87,88] or somewhat worse [82] than their pretransplant state. In one recipient, only mild glucose intolerance was reported even 7 years after the autotransplant [86]. But, in recipients who required insulin therapy before the autotransplant, no improvements in glucose metabolism could be expected. The question, then, was whether such patients should undergo a transplant in the first place. However, at the time it appeared that autotransplants may have helped some recipients retain minimal insulin and glucagon function, resulting in a less brittle form of diabetes mellitus than that of patients who underwent total pancreatectomy alone.

In 1990, Rossi et al. presented long-term results in 13 patients who had undergone extensive pancreas resection and simultaneous segmental autotransplants (median follow-up, 62 months). Of the 13 recipients, 11 had technically successful grafts: three of 6 who underwent total pancreatectomy and 3 of 5 who underwent near-total resection remained insulin independent. Those who required insulin required small doses and had stable diabetes. However, the rate of pain recurrence was higher in those who underwent near-total resection and, for that reason, total pancreatectomy as the initial procedure of choice was favored. Rossi et al. concluded that total pancreatectomy and simultaneous segmental autotransplants offer definitive, although at times transient, benefits in glucose metabolism, as compared with total pancreatectomy alone [90].

In his last overview, published in 2003, on pancreas autotransplantation in patients with chronic pancreatitis, Rossi lists a total of 28 such procedures: in 25 of them the femoral vessels and in 3 the iliac vessels were used for anastomosis; in 17 procedures, the pancreatic duct was obliterated, in 11 ligated and in 1 enteric-drained. There was 1 operative death; 5 patients developed pancreatic fistulae, 5 patients necroses, 3 patients abscesses. Remarkably, 16 of 28(57%) patients remained insulin-independent, 19 of 25(76%) were pain-free and in another 5(20%) the pain improved [91]. If islet processing and yield improvement had not occurred in the 1990s, pancreas autotransplantation may still be around.

Pancreas autotransplants for malignancy

Pancreas autotransplants even for small pancreatic malignancy are no longer performed. If an auto-transplant is performed at all at an early pancreatic tumor stage, it would be an islet autotransplant.

In the past, heterotopic segmental autotransplants after total pancreatectomy were reported in few patients with periampullary cancer or advanced gastric cancer. In 1983, McDonald et al. described a 73-year-old patient with a movable mass (3 to 5 cm) in the pancreatic head. At the time of resection, no positive lymph nodes were noted and the distal pancreas was tumor free. The distal pancreas was removed in vivo, the pancreatic duct was ligated, and the distal pancreas was autografted into the thigh. Tumor recurrence was not reported, but follow-up time was only 8 months [92]. In a second patient with advanced periampullary cancer, the segmental pancreas autograft was also anastomosed to the left femoral vessels. On completion of total pancreatectomy, the distal pancreas was noted to be free from cancerous invasion. The pancreas was transected at the pancreatic body, 3 cm away from the tumor; cold ischemia time was 105 minutes. Posttransplant, insulin requirements decreased and insulin administration was discontinued at 5 months [93].

Tersigni et al. described three irradiated segmental pancreas autotransplants in patients with cancer of the pancreatic head [94]. The autografts with ligated ducts were irradiated with 2,000 to 5,000 rad, doses believed to not affect β- and α-cells. After irradiation, the tumor-free distal segmental pancreases were autotransplanted by anastomosing the splenic vessels to the common femoral vessels. The first graft (5,000 rad) became necrotic and was removed 2 weeks posttransplant; the second and third autografts (2,000 rad each) were functioning and the patients were insulin independent at 7 months and 1 month posttransplant, respectively. High-dose irradiation was used to (1) completely destroy any remaining multicentric tumor foci in the distal pancreas and (2) decrease exocrine secretions. However, the two patients with functioning autografts subsequently developed abdominal metastases and, after beginning chemotherapy, had to resume insulin. Despite irradiation, denervation, and the heterotopic location of the autograft, both patients' intial plasma, insulin, and glucagon levels were within normal range; responses to oral GTTs and IV arginine stimulation tests were normal [95].

In another series, nine patients with advanced gastric cancer underwent total gastrectomy, total pancreatectomy, and simultaneous segmental pancreas autotransplants with anastomosis of the splenic vessels to either the external iliac or common femoral vessels. Pancreatic exocrine secretions were managed by external, enteric, or bladder drainage. A total of four grafts were lost because of surgical complications (venous thrombosis, leakage), but five recipients remained insulin independent (follow-up, 7 to 41 months) [88].

On another historical note, in 1970 Urea et al. described allotransplanting a pancreatic insulinoma into the thigh of an insulin-resistant patient with juvenile diabetes mellitus. Although the 17-year-old recipient was aglycosuric for 47 days, insulin independence in the absence of immunosuppression was never achieved [96] It is obvious from the above (anecdotal) reports with short follow-up that segmental pancreas autotransplants in patients undergoing total pancreatectomy for malignancy were extremely rare even in the pre-islet autotransplant era. The possible presence of occult pancreatic cancer cells in all types of pancreatic autografts (segments or islets) is a major concern.

This controversial issue is confirmed by the Milan group in a 2024 article that reported their experience in 75 patients with malignant pancreatic neoplasms who underwent an islet autotransplant after total or subtotal pancreatectomy. On follow-up, they noted metastatic liver and lung disease in 17 (23%) patients [99]. Further insights must be gained before even islet autotransplantation can be recommended routinely for patients undergoing resection of a pancreatic malignancy.

Pancreas transplants as part of cluster transplants for upper-abdominal malignancies

In 1989, Starzl et al. reported on abdominal organ cluster transplants for the treatment of upper-abdominal malignancies [97]. However, long-term outcome was poor due to a high cancer recurrence rate. Starzl summarized it best by stating that "the marriage of transplantation and therapeutic oncology has been troubled" [97] -"troubled" both by the necessity of administering immunosuppressive therapy and by the natural behavior of upper-abdominal malignancies.

The field of pancreas transplantation after total pancreatectomy continues to evolve. Generette et al. in 2020 reported on a case of en-bloc liver and pancreas allotransplantation after total pancreatectomy with autologous islet transplantation. The patient with intractable and debilitating pain secondary to chronic pancreatitis had initially undergone a TPIAT. Subsequently, the patient developed alcohol related acute liver failure and en-bloc liver and pancreas transplantation was performed to replace the failing liver with engrafted islets. A successful pancreas transplantation was performed to resolve his life-threatening severe hypoglycemic episodes [98].

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