

Total Pancreatectomy with Islet Auto-Transplantation for Treatment of Refractory Chronic Pancreatitis

► Gastrointestinal and transplant surgeons, gastroenterologists, and endocrinologists at Penn Medicine are performing total pancreatectomy with islet auto-transplantation (TPIAT) for treatment of refractory chronic pancreatitis.

Chronic pancreatitis (CP) is defined by severe and irreversible pancreatic parenchymal damage attended by progressive interstitial fibrosis and varying degrees of exocrine and endocrine dysfunction. The disease is provoked when inflammation or obstruction of the pancreatic duct prevents the escape of pancreatic enzymes into the gastrointestinal tract, leading essentially to self-digestion.

Complications include intractable pain, nutrient maldigestion, pancreatogenic diabetes, steatorrhea, necrosis and an increased likelihood for pancreatic ductal adenocarcinoma. Concurrent complications in adjacent organs, including stenoses of the duodenum, bile duct and portal vein, are not unusual.

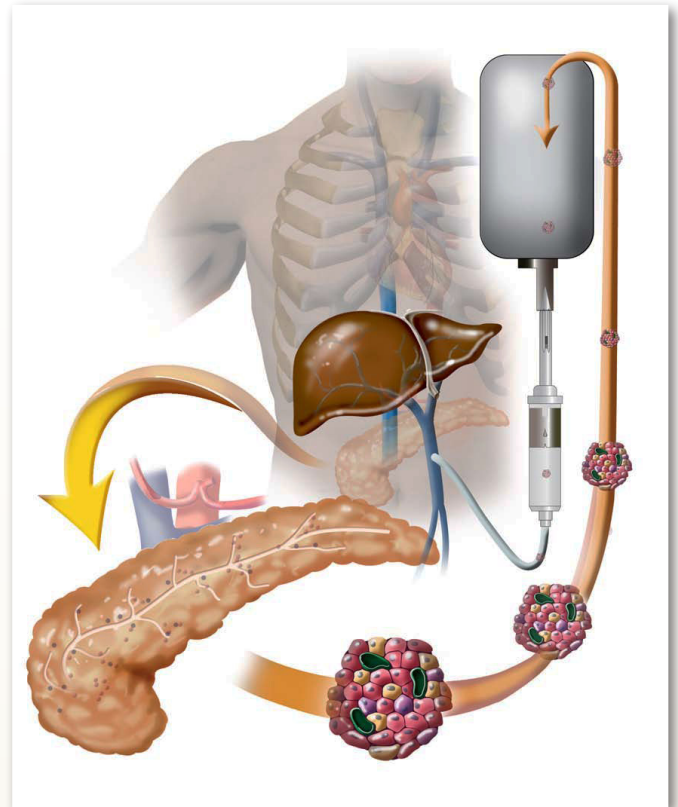
Treatment: Currently, there is no durable medical treatment for the inflammation or fibrosis associated with CP. Treatment is thus largely palliative, consisting of enzyme supplementation, somatostatin analogues and antioxidants with opioids supplemented, when necessary, by nerve blocks for potential pain management. The efficacy of these treatments generally diminishes over time.

Patients who are refractory to medical treatment for progressive chronic pancreatitis with pseudocysts are candidates for endoscopic decompression, and beyond this, for strategic partial resection of the pancreas or total pancreatectomy. The latter is identified with complete loss of exocrine and endocrine function resulting in pancreatic exocrine insufficiency and brittle surgical diabetes.

Outside of these impositions, improvement in quality of life is typically quite good following total pancreatectomy, with the majority of patients reporting substantial resolution of pain, and cancer risk is eliminated. Efforts to further enhance the post-surgical experience for patients having pancreatectomy have thus focused on sustaining pancreatic endocrine function through isolation of the islet cells from the diseased pancreas for auto-transplantation back in the patient's liver.

TPIAT is performed at Penn Medicine by a multidisciplinary team comprising endocrinologists, gastroenterologists, surgeons and pain specialists. By infusing the patient's own islet cells, TPIAT avoids the need for immunosuppression. In 5-year prospective studies, patients having TPIAT have consistently reported improvement in quality of life, with the majority (about two-thirds) reporting narcotic independence within one year; insulin independence occurred in a minority of patients (about one-third) and waned over time in these studies, but glycemic control was substantially improved. [1]

[1.] Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, Schwarzenberg SJ, Lowe ME, Rickels MR, et al. *Pancreatology*. 2014;14:27-35.



► **Figure 1:** Total pancreatectomy with islet auto-transplantation (TPIAT) involves separation and purification of islet cells from the diseased pancreas for transplantation via portal vein infusion into the patient's liver.

Case Study

Mr. G, a 39-year-old man, was referred to the Divisions of Gastrointestinal Surgery and Transplant Surgery at Penn Medicine for evaluation of chronic pancreatitis. Mr. G's medical history included tobacco and alcohol abuse, cholelithiasis treated by cholecystectomy and recurrent episodes of pancreatitis requiring six hospitalizations in the past year and leading to a dependence on opioids. An endoscopic decompression of the pancreas shortly after his 37th birthday provided a transient improvement in pain, which he described as unremitting and particularly excruciating during exacerbations of pancreatitis. He has been on medical leave from work for the past year and is deeply concerned about his future job security.

Mr. G's lab workup revealed elevated serum pancreatic enzyme levels during episodes of pancreatitis and normal fasting glucose and HbA1c. A fecal elastase was consistent with pancreatic exocrine insufficiency, and an oral glucose tolerance test excluded diabetes. An abdominal CT scan demonstrated pancreatic fibrosis and ductal stenosis.

At this point, Mr. G began pancreatic enzyme replacement to treat his exocrine insufficiency. Because his endoscopic decompression had been ineffective, and with no significant dilation of the main pancreatic duct that might be amenable to surgical decompression, he consented to have a TPIAT procedure to alleviate his pain and improve his quality of life. He was counseled that total pancreatectomy would produce surgical diabetes and that the hoped-for goal of islet auto-transplantation was to prevent or significantly ameliorate this concern.

(Case study continued on back page)

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In addition, Mr. G was instructed in the use of a multi-dose insulin injection regimen that would be required for at least a few months post-operatively. Because splenectomy is required as part of a total pancreatectomy due to its shared blood supply, he also received vaccination against pneumococcus, *H. influenza*, and meningococcus.

Mr. G was admitted to the hospital in the morning for surgery. Under general anesthesia, an open total pancreaticoduodenectomy was performed with splenectomy, and the pancreas was immediately separated and brought to the islet isolation facility in the adjacent building.

While Mr. G underwent choledochojejunostomy and gastrojejunostomy, the pancreas was collagenase digested and the islet cells separated from the acinar and ductal tissue by centrifuge purification. The isolated islets cells were brought back to the operating room and using the splenic vein stump were infused in the portal circulation for delivery throughout the liver parenchyma. Medial management included prophylactic antibiotics, cautious anticoagulation, and insulin to maintain normoglycemia during the period of islet engraftment.

Following surgery, Mr. G was monitored in the intensive care unit for three days until his anticoagulation and insulin was transitioned to subcutaneous administration. His diet was advanced, and he remained under observation in a routine hospital room until discharge on the tenth day post-operatively. The pain service managed his post-operative comfort and prepared Mr. G for post-discharge weaning from narcotics.

By the third post-operative month, Mr. G had healed from surgery, had been tapered off narcotics, was tolerating his diet while taking his prescribed pancreatic enzymes, and was maintaining normal glucose levels and HbA1c while taking only once daily long-acting insulin. By the sixth post-operative month, Mr. G had tapered off his insulin and continued to maintain normal glucose control.

Access

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Faculty Team

Penn Medicine is among a handful of medical centers nationwide with an FDA-compliant current Good Manufacturing Processes (cGMP) facility for the isolation and transplantation of islet cells and the combination of services, specialties and experience required to perform TPIAT. Home to both the Penn Transplant Institute and the Institute for Diabetes, Obesity and Metabolism (IDOM), Penn receives support from the National Institute for Diabetes and Digestive and Kidney Diseases for its Diabetes Research Center and Center for Molecular Studies on Digestive and Liver Diseases. Penn is also a member of the Clinical Islet Transplantation (CIT) Consortium, a network of NIH-supported clinical centers conducting pivotal studies of islet transplantation for patients with type 1 diabetes.

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