

## Total Pancreatectomy and Islet Auto Transplantation for Chronic Pancreatitis

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Chronic Pancreatitis (CP) is a condition associated with irreversible functional and morphological abnormalities from long term inflammation and fibrosis [1]. Endocrine and exocrine dysfunction results in the diseases profound morbidity.

The endocrine dysfunction deserves a special mention as it results in diabetes, often referred to as, *brittle diabetes*, because of the management difficulty. Along with a spectrum of hyperglycemia, lethal hypoglycemic episodes are common in these patients. The incidence of overt diabetes in patients with CP is approximately 20%, however up to 70% have altered glucose metabolism [2]. In a series by Gall et al. [3] of patients undergoing total or partial pancreatectomy, half of late deaths were due to iatrogenic hypoglycemia [3]. Hypoglycemia has become an interesting topic as it has been shown that islet transplants result in a profound improvement in hypoglycemic episodes for many patients even if the recipient did not achieve insulin independence [4]. Although, malabsorption and statorrhea can be treated with pancreatic enzyme replacement and diabetes can be treated with insulin, pain management is an extreme challenge.

Pain is a common feature for patients; approximately 85% of patients will develop pain at some point during the course [5]. The severity and characteristics of pain have a major impact on CP management. Most implement a combined approach to treatment including narcotics, non-narcotic analgesics, anti-depressants, and neuropsychiatric medications [6]. Eventually, however some patients go on to undergo surgical resection for intractable pain or opioid dependence [7]. Although, total pancreatectomy is a relatively rare surgery for patients with CP, it has become increasingly popularized due to the improvements in Islet Auto Transplantation (IAT).

In isletallogenic transplantation for patients with type I diabetes, there have been substantial improvements in standardizing islet processing such that primary efficacy has improved in the years between 2007 and 2010 compared to those that were transplanted between 1999 and 2006 in islet allogeneic transplantation. Insulin independence, according to a study published in 2012, was 44% at year three post-transplant during 1999-2006 compared to only 27% in years past [8-13]. The Collaborative Islet Transplant Registry (CITR) accumulates the most comprehensive collection of data regarding islet allogeneic transplants in North America, Europe, and Australia. As of 2008 there have been 325 adult recipients of islet transplants. The CITR reports that the number of severe hypoglycemic events and the glycated hemoglobin levels were significantly improved in those undergoing transplantation.

Substantial improvements in islet processing developed in isletallogenic transplantation contribute to promote IAT as a more reasonable therapeutic option for patients with CP [14]. Sutherland et al. [15] reported on a single institution review of 409 patients undergoing IAT after total pancreatectomy between 1977 and 2011. At three years, approximately 33% patients were insulin independent; another 33% had partial islet function. Moreover, many of these patients were narcotic free at three years and reported improved quality of life scores post-surgery [15]. Dong and authors compiled a systematic review for all patients undergoing AIT after total pancreatectomy [16]. There

were a total of 15 observational studies included, 11 studies included 354 patients that underwent IAT after a total pancreatectomy for CP an additional two studies was done after a partial pancreatectomy and two studies included both. Despite the authors mention of poor quality studies including; single centers, small sample size, and suboptimal data gathering, they were able to conclude overall insulin independence for 15.57 months with a long term mortality of 0.7 to 1.38 per 100 person-years. Overall, there appears to be a benefit to IAT with minimal long term mortality.

More recently, a case report out of the University of Arizona, discusses a completely robotic total pancreatectomy with IAT for a woman with CP [17]. The operation was 690 minutes and resulted in 157,000 islet equivalents infused. The patient was discharged requiring no basal insulin and a mean glucose of 108 after 1 month post IAT.

There is significant evidence to support the correlation between islet yield and insulin independence [18]. Likewise, the longer a patient has suffered with CP, the more difficult it is to isolate islets. As such, after all medical options have been tried it may be of benefit to refer these patients early for surgery. This position was echoed by Ong et al. [19] which stated that early surgery could reduce the operative risk by reducing the level of fibrosis and adhesions of the pancreas and would maximize the islet yield and increase the potential towards insulin independence [19].

Currently, the biggest concern is the lack of centers performing IAT and the cost required to isolate islets. In a study by, Morgan et al. [20] he reviewed the outcomes and costs associated with intra-operative islet infusion versus percutaneous transhepatic infusion. The cost of the percutaneous route was determined to be a more cost effective model and will likely help to drive down overall IAT costs [20]. More importantly, improvement in chronic pain for patients and independence from narcotics has large quality of life and job retention implications. The direct health care costs of CP are difficult to quantify given the variable and protracted course of CP. In a German series, the average total hospital stay for each patient admitted for CP was 18 ± 13 days. Of the patients reviewed 34% took narcotics daily, 57% took enzyme replacements, and 25% took injectable insulin [21]. Likely, the total cost of total pancreatectomy with IAT would be similar to the total cost of CP management over time however; we could not find a study that specifically looked at these variables.

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Based on these reports it appears that total pancreatectomy with IAT is a feasible procedure with good outcomes and patient satisfaction. Insulin independence rate post total pancreatectomy and IAT is fair however, may be improved with patient selection, earlier operations, and standardized islet isolation protocols.

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