REVIEW

Diabetes Management

Islet autotransplantation: past, present and future. Chapter II: the role of islet autotransplantation for the treatment of chronic pancreatitis

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Practice points

- Chronic pancreatitis (CP) is a progressive disease characterized by an irreversible damage inflicted to the pancreas. It is associated with varying degrees of inflammation, fibrosis, increased risk of neoplasms and alterations to the exocrine component of the pancreas, with the varying involvement of islets of Langerhans.
- With time, available therapy becomes ineffective and can no longer relieve the progressive chronic pain associated with CP.
- The goal of near-total pancreatectomy or total pancreatectomy (TP) for CP, and other pancreatic disorders, is to alleviate the intractable pain inflicted by CP in patients who fail other forms of treatment approaches.
- Near-total pancreatectomy and TP alone result in insulin and glucagon deficiency, as well as surgically induced insulin-dependent pancreatogenic diabetes with poor metabolic control.
- Patients with pancreatogenic diabetes may have wide daily glycemic excursions and hypoglycemia due to endocrine failure and exocrine deficiency. Glucagon and insulin deficiency, and poor metabolic control are often difficult to manage.
- Islet autotransplantation (IAT) following pancreatic resection is performed as the prophylaxis for iatrogenic diabetes which often develops following pancreatic resection, near-total pancreatectomy or TP.
- IAT is demonstrated to improve pain, alleviate the risk of 'brittle diabetes' and offers freedom from exogenous insulin in a large number of patients. Approximately 40% of these patients are able to achieve insulin independence. In addition, diabetes control in recipients of IAT is superior to those patients who are not transplanted.
- IAT represents a reasonable therapeutic option for the treatment of glycemic disorders in a wide range of the population, which includes children as well as elderly patients.

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SUMMARY The most successful islet transplants have been performed in non-autoimmune diabetes patients, in an autologous setting, in conjunction with total or near-total pancreatectomy for the treatment of pancreatic or hepatobilliary conditions. The primary goals are the treatment of an underlying disease and relief of persistent pain. Islet autotransplantation is important in this setting. Following islet autotransplantation most patients maintain good glycemic control, with ~30–40% able to discontinue insulin therapy. Transplantation of high islet mass is associated with higher C-peptide, in-range HbA1c and insulin independence. Strategies to increase the proportion of insulin independent patients and long-term engraftment include islet isolation, curtailing the innate immunity-associated events and β-cell apoptosis, and alternative transplant sites. Future studies are of benefit. Chapter II discusses the role of islet autotransplantation in the treatment of chronic pancreatitis.

KEYWORDS
• chronic pancreatitis
• diabetes • insulin
• islet autotransplantation
• pancreatectomy
• transplant

This is the second chapter of the two-part review that covers past experiences and future directions of islet autotransplantation (IAT) for the treatment of chronic pancreatitis (CP) and other pancreatic disorders [1].

CP is a disease characterized by a progressive, irreversible damage to the pancreas and is associated with varying degrees of inflammation, fibrosis, increased risk of neoplasms and alterations to the exocrine component of the pancreas, with the varying involvement of islets of Langerhans. With time, available therapy becomes ineffective and can no longer relieve the progressive chronic pain associated with CP. The goal of near-total pancreatectomy or total pancreatectomy (TP) is to alleviate the intractable pain inflicted by CP in patients who fail other forms of treatment approaches. Near-total pancreatectomy and TP alone result in insulin and glucagon deficiency, as well as surgically induced insulin-dependent pancreatogenic diabetes (PD) with poor metabolic control. Both glucagon and insulin deficiency and poor metabolic control are often difficult to manage. Patients who have PD (also known as 'iatrogenic diabetes') may have wide daily glycemic excursions and unpredictable hypoglycemia not only due to endocrine failure, but also exocrine deficiency. IAT offers a valuable addition to the surgical resection of the pancreas for the treatment of CP and other rare pancreatic disorders. IAT following pancreatic resection has been demonstrated to improve pain, alleviate the risk of 'brittle diabetes' and offer freedom from exogenous insulin in a large number of patients.

Although pancreatic islet transplantation is commonly associated with the treatment of Type 1 diabetes mellitus (T1DM), transplantation of islets of Langerhans does have a wider application. In fact, to date the most successful islet cell transplants have been performed in patients without autoimmune and/or pre-existing diabetes. Most of these transplants have been done in an autologous setting, in conjunction with near-total pancreatectomy or TP for the treatment of either benign or malignant pancreatic, or hepatobilliary conditions. The primary goal in such cases is the treatment of an underlying pancreatic disease and relief of persistent pain often associated with acute relapsing pancreatitis, CP, neoplasms and other rare pancreatic disorders. IAT is important in the setting of near-total or total surgical resection of the pancreas. It is performed as the prophylaxis for iatrogenic diabetes which often develops following pancreatic resection, near-total pancreatectomy or TP. IAT following near-total or TP to treat CP was first performed in 1997 at the University of Minnesota (UMN); the goal of this treatment was to prevent or minimize PD by preserving beta cell mass and insulin secretory capacity [2–4].

The idea for IAT evolved from the islet allograft experience and the desire to understand the differences in metabolic outcomes between islet autografts in pancreatectomized patients and islet allografts performed to treat T1DM. The latter often failed, and it was necessary to understand if islet allografts failed as a result of technical challenges associated with the islet isolation process, or for immunologic reasons [5].

There is a plethora of literature that demonstrates that IAT in the setting of TP results in C-peptide production in the majority of patients receiving islet autografts; with ~40% of these patients are able to achieve insulin independence. In addition, diabetes control in recipients of IAT is superior to those patients who are not transplanted [5–7].

When compared with allogeneic islet transplantation, IAT has several advantages in terms of long-term success. In contrast to islet allotransplantation, there is no autoimmune disease directed specifically against beta cell or allogeneic rejection to the transplanted donor graft; there is no need for immunosuppressive drugs, demonstrated to be diabetogenic and even toxic to beta cells. Another difference between IAT and allogeneic islet transplant recipients is that the former utilizes islets that are usually isolated within 3–4 h of pancreatic resection, as opposed to the longer periods of time required to isolate allogeneic islets from deceased heart-beating donors. Hence, for the purposes of IAT the organ is not exposed to prolonged cold ischemia time (CIT) known to negatively impact the pancreas and impair cell viability and function [8]. Furthermore, it has been proposed that pancreata resected as a result of CP might contain more islet progenitor cells found in pancreatic ducts [9].

With longer life expectancy, the number of patients undergoing pancreatic resection is growing. Due to the fact that IAT is a minimally invasive procedure, associated with low morbidity and results in significant improvements in quality of life (QOL), it represents a reasonable therapeutic option for the treatment of glycemic disorders in a wide range of the population, which includes children as well as elderly patients.

Islet autotransplantation

First introduced in 1997 at the UMNIAT has been performed following TP or near-total pancreatectomy done to alleviate the pain associated with CP, in patients who failed other forms of treatment. The main centers to perform IAT following TP remain UMN, University of Cincinnati and the University of Leicester [10].

Initially, it was postulated that IAT could preserve the β-cell mass and insulin secretory capacity required to maintain metabolic control, in order to prevent or minimize the otherwise inevitable PD. Although IAT has been performed following pancreatic resection for premalignant and malignant neoplasms, the main application of TP-IAT is for treatment of the intractable pain associated with CP. The review of the literature demonstrates that hyperglycemia due to TP can lead to islet cell dysfunction and failure of engraftment [10–12]. Therefore, to minimize the insulin secretory demand from the freshly infused islets and to achieve euglycemia, exogenous insulin drip administered during pancreatectomy and after IAT is recommended [13]. When the patient begins to eat, a transition to subcutaneous insulin is made. In many patients, however, insulin is gradually withdrawn, but not before approximately 6 months following surgery and IAT.

At the present time, the pancreatectomy is often performed by an open laparotomy, with the robotic approach to the latter described more often [10,14]. The main goal during surgery is to preserve the blood supply to the pancreas, in order to minimize ischemia of the pancreatic parenchyma. Following removal, the organ is placed in cold organ/tissue preservation solution, normally University of Wisconsin solution and packaged for transport to the islet isolation facility. The goal of the isolation is to separate the endocrine component of the pancreas – insulin producing islet cells – from the exocrine tissue, so that the former can be administered to a patient via the intraportal infusion [11].

It was Paul Lacy, who was the first to demonstrate that rat islets could be successfully isolated and transplanted [15]. Several years later, Mirkovitch and Campiche were the first to successfully transplant free islet grafts by injecting the dispersed graft into the spleen of pancreatomized dogs [16]. David Sutherland, working at the UMN, was first to attempt IAT in human subjects, to prevent PD following near-total pancreatectomy and TP [10,11]. Although first series of transplants were technically successful, the results were largely inconsistent. A loss of function was reported in several patients several months following IAT [10,11]. Early challenges were corrected by significant improvements in surgical care and islet isolation technique.

C Ricordi's automated method for islet isolation, first published in 1988, pioneered a significant improvement in the islet isolation process. It allowed for the continuous release of the islets liberated from the exocrine tissue during the digestion phase, thereby protecting them from any further enzymatic action and preventing overdigestion of the endocrine tissue. By significantly reducing the islet cell loss during the digestion process, this innovation ultimately resulted in significant improvement to both quality and quantity of the islet tissue [17]. The digestion process was judged complete when only ductal tissue was left in the chamber, with no or small amount of pancreatic tissue remaining. The fact that Arch. Surg. method resulted in the complete dissociation of pancreatic tissue, with a significant improvement to the quantity and quality of the isolated islet cells, set this method apart from what was done and published previously [17].

New and improved enzyme blends, effective use of large-scale purification methods and routine application of a number of additives during the islet isolation process all contributed to further improvements in the islet isolation yield and quality of the isolated cells, as well as the utilization of the isolated tissue for transplant [18–23].

Of substantial benefit is the fact that islet preparations for IAT are transplanted fresh, that is, immediately following isolation.

The US FDA recommends that islet cell processing should be done in a Good Manufacturing Practices (GMP) laboratory that meets all of the FDA criteria [24]. Although these recommendations have been made for allogeneic islet products transplanted under the auspices of current GMP (cGMP, 21 CFR Part 210 and 211), New Investigation Drug Application (IND, 21 CFR Part 312) and regulations for biologics (21 CFR Part 600, 601 and 610), it is good practice to follow these recommendations for autologous islet cell processing as well [10].

• Islet isolation & infusion

The length of time between removal of the pancreatic tissue and islet transplantation is approximately 3–4 h in most cases. Generally, total pancreatectomy, islet isolation and islet infusion are performed at the same location and/or the same center. Therefore, excised pancreas is exposed to a relatively short CIT, that is, lesser than that for allogeneic islet transplantation [3]. Immediately following the removal of the pancreas, islet cells are isolated in a procedure similar to islet isolation from deceased donors. The procedure consists of several steps that include cleaning and cannulation of pancreas, organ perfusion and distention, digestion, dilution and collection, and islet cell purification using density gradients [17,25,26].

Following the resection of the pancreas, the latter is cleaned of excess fat and connective tissue, and the pancreatic duct is cannulated using a standard 16G angiocatheter. The organ is then perfused with the enzymatic solution, prepared while the pancreas is cleaned, and dispersed during the digestion step performed following the Arch. Surg. automated method [17]. The purification step aims at enriching the final product with endocrine tissue, while reducing the volume of the exocrine component, hence reducing the volume of the final preparation designated for an infusion in a recipient's liver [17]. Islet purity is a subjective evaluation performed by visual assessment. The quantity of dithizone-stained islets which stain dark red is compared with unstained acinar tissue [27]. Purification of the endocrine fraction is not an obligatory step in the process of islet isolation for IAT. In fact, Webb *et al.* demonstrated that in IAT, islet purification does not have an impact on insulin independence [28]. UMN does not purify islet preparations to maximize the islet yield, for products with low tissue volume obtained from fibrotic pancreata [10,29]. In some cases, high-volume digests that contain a large number of mantled islets (islet cell surrounded by a light ring of acinar tissue) are not purified either, in order to avoid islet loss, as mantled islets have been reported difficult to purify without a nominal loss [30]. During purification, at least 40% of islet cell mass is normally lost; however, this is lower than the amount that would need to be discarded if purification was not performed as part of the isolation process [31]. Hence, it is recommended to purify all or part of the islet preparation whenever the crude tissue digest volume exceeds 15 ml, to prevent any undue rise in portal pressure during the embolization in the liver [30,32]. Kobayashi *et al.* reported that purification with COBE 2991 Cell Processor (Cobe BCT, CO, USA) was performed whenever the digest volume exceeded 20 ml, with the average tissue obtained for intraportal infusion of 13.2 ± 10.2 ml [31]. There have been reports where part of the islet preparation was placed in an alternate site, such as sub-mucosal layer of the stomach and peritoneal cavity, when portal pressure during the islet infusion reached 20–30 cm of water [30,33]. Correction of the tissue volume for patient's body weight was found to significantly improve the predictive ability of the model of portal hypertension based on tissue volume [30,33]. However, due to the fact that in IAT, there is no possibility of selecting a donor for favorable BMI, age and underlying disease prior to the surgical manipulation of the pancreas, the decision as to whether or not to purify a given islet preparation should rest with the surgeon and the isolation team. The priority here is to obtain the most optimal islet mass.

In preparation for infusion islet cells are suspended in a 50:50 solution of 20% human serum albumin and transplant media, which is CMRL-1066 supplemented with a number of supplements, which wary depending on the transplant center. Islet cells are normally infused into the liver via the portal vein, by gravity. The cells are normally returned to the patient fresh – without the need for culture – while the patient is still in the operating room, with an open incision. On average, islet autograft isolation and preparation for infusion should take approximately 3 h [10,11].

Infusion of a significant volume of tissue into the portal vein can culminate in a marked reduction in blood flow, intraportal thrombosis brought on by tissue thromboplastin present in the islet graft and elevated portal pressure. To avoid these risks intravenous heparin anticoagulation therapy is administered immediately prior to islet infusion or with the final islet product [34]. The dose of heparin is normally closely monitored, as over the years heparin-induced thrombocytopenia has been reported in a number of patients [35]. Islet cells are infused slowly, over 15–60 min, while the infused tissue volume and patient's portal pressure are closely monitored. Portal pressure must be evaluated at baseline, that is, prior to the infusion, at the time of product infusion, and 15–20 min after the completion of the infusion, in order to obtain peak portal pressure. Imaging, such as duplex ultrasound or computed tomography, is often utilized to evaluate the liver during and immediately following islet infusion [30,33].

Doppler ultrasound studies demonstrated a ~4% incidence of portal vein thrombosis in islet allograft recipients, with the former closely associated with the volume of transplanted tissue and degree of anticoagulation in the early post-transplant period [32]. In IAT patients, portal vein thrombosis is occasionally detected on ultrasound, but it has been reported as clinically insignificant [10]. Although heparin administration has proven to be an affective anticoagulation therapy, continuous administration of heparin in combination with portal hypertention increase the risk of perioperative bleeding [10,11]. Minimizing the tissue volume at the time of infusion, and, therefore, lowering portal pressure, significantly reduces the possibility of bleeding. It has been reported that the risk of clinically-significant bleeding is <8%, when change in portal pressure level does not exceed 25 cmH_2O, and tissue volume is reduced to <0.25 ml/kg [35,36]. At the present time, the tendency is to purify the islet preparation so that the final tissue volume is reduced to a volume well-tolerated by the portal vein, hence avoiding any rise in portal pressure, while circumventing the necessity to discard any part of the preparation [10,11]. Hepatic enzymes show a transient rise during the early post-infusion period, but without any indication for future hepatic dysfunction [29]. Imaging studies of the liver during the immediate post-infusion period often show benign changes such as echogenic nodularity, but these are unrelated to clinical problems [3,37].

• Route of administration

Technically speaking, the simplest and the most cost-effective technique to deliver the islets are to infuse them directly into the portal vein, in the operating room, before the patient is closed following TP. However, the portal system can be also accessed via a re-canulized umbilical vein, middle colic or mesenteric vein, temporarily exteriorized omental vein, and transhepatically [33,37–39]. The percutaneous transhepatic approach has been described by Morgan *et al.*, but found to be less cost-effective compared with delivering the islets directly into the portal vein in the operating room [40]. However, the fact that the abdomen cannot be inspected for bleeding following heparinization and possible increase in portal pressure never made the transhepatic approach popular.

Predicting islet yield from organs obtained by pancreatectomy in CP patients, both adults and children, is difficult. The final islet yield seems to be related to the severity of CP and the associated gross pancreatic morphology, as well as the type of pancreatic resection and prior surgical procedures [31]. For example, severely fibrotic pancreata obtained from pediatric patients, in which ductal neogenesis is observed, and patients with higher BMI are consistently associated with high islet cell yield. At the same time, islet yield from adult organs, where nesidioplastosis is present on histopathology, is low. Kobayashi *et al.* confirmed these results when they investigated the relationship between histopathologic findings such as degree of fibrosis, acinar atrophy, inflammation and nesidioblastosis, islet cell yield, and resulting graft function [31]. He examined 105 patients who underwent TP followed by IAT, with the median number of 2968 islet equivalents (IEQ)/kg of islet cells infused. The authors reported that while fibrosis, acinar tissue atrophy and inflammation had a negative correlation to the islet yield, the latter correlated positively with graft function [31].

Accumulated data from animal studies and that from clinical results demonstrate that the most common and efficient site for islet engraftment is the liver, with the islet cells infused into the liver by cannulation of the portal vein (intraportal infusion) [41,42]. Other sites, however, such as the renal capsule, spleen, omentum, kidney, subserosa and peritoneal cavity, have been evaluated with the hope of avoiding risks associated with intraportal infusion, impacting both the patient and the function of the islet graft [41,43–44]. Intrasplenic islet transplantation resulted in insulin independence in an animal model; however, splenic infarction and venous thrombosis were reported in human subjects [45–48].

A recent clinical case of an intramuscular IAT after a TP due to hereditary pancreatitis in a 7-year-old girl was reported in Sweden [49]. This case was characterized by a high yield cell yield, that is, 6400 IE/kg that usually results in insulin independence when the islets are infused to the liver. In this case, at 2-year follow-up the patient remained on low dose insulin therapy, but without recurrent hypoglycemia and a clearly positive C-peptide [49]. In another pilot study, autologous islet cells were transplanted in the bone marrow (BM) of four patients with PD and hepatic contraindications for islet infusion in the portal vein. The islets were infused in the iliac crest BM, in the operating room, immediately after surgery; using the same procedure utilized for the administration of cord blood cells in patients with acute leukemia [50]. In all four recipients, islet cells engrafted successfully, as demonstrated by a measurable post-transplant C-peptide levels and histopathological evidence of insulin producing cells and molecular markers of endocrine tissue in BM biopsy samples. No adverse events associated with either the infusion procedure, or the presence of islet cells in the BM. At 944 days of follow-up, the authors reported sustainable islet graft function [50].

Regardless of the implantation site, in the immediate post-infusion period, islet cells survive by naturally-occurring nutrient exchange. During this period islets have reduced functional capacity, which does seem to improve with vascularization. There is a direct correlation between the weight of the patient and the number of islet equivalents required for successful engraftment. This, however, is not necessarily true for the functional outcome. Sutherland *et al.* (2008) reported ~7% of IAT recipients who received <2500 IEQ/kg of patient body weight becoming insulin-independent, compared with one-third of patients receiving >5000 IEQ who do not [4,7]. This phenomenon might be related to the size of the islet graft, as well as the differences in viability between different islet preparations; in other words a low islet yield graft with more viable cells results in a superior functional output compared with a high islet yield graft with fewer viable cells. This hypothesis is supported by the studies conducted by Pappas *et al.*, which demonstrated that a good predictor of the islet graft function in IAT patients was an *in vitro* oxygen consumption rate [51].

• Metabolic outcomes of pancreatic resection followed by IAT

There is no guarantee that IAT following pancreatic resection or TP is successful; hence, patients must be willing to accept the possibility of developing post-surgical diabetes as a tradeoff for alleviation of retractable pain, discontinuation of narcotics for pain management and improved QOL. Preservation of native β-cell mass and insulin secretory capacity in this patient cohort is a desirable, albeit secondary outcome; a priority being the management of pain, as already discussed elsewhere in this chapter [4,10–11,52]. However, a number of reports indicate that IAT is capable of preserving endogenous β-cell function (C-peptide positivity) in 70–90% of recipients therefore preventing the development of 'brittle' diabetes in majority of recipients [10,52–54].

Patients should perform home blood glucose monitoring. Monitoring of islet function include fasting plasma glucose levels, postprandial plasma glucose levels, hemoglobin A1c (HbA1c) and stimulatory tests (oral glucose or mixed meal tolerance tests) with measurement of glucose and C-peptide levels may also be considered to monitor islet function over time. Mixed meal tolerance test is a dynamic test to evaluate stimulated C-peptide secretion, and has been reported to correlate with the number of islet cells transplanted [52]. The literature shows that at 3-year follow-up approximately 90% of the patients were C-peptide positive, with 82% of the patients demonstrating HbA1c of <7.0, regardless of the islet dose [52]. At the same time, stimulated C-peptide level was higher in patients who received >5000 IE/kg versus those receiving 2500–5000 IE/kg and <2500 IE/kg ($p < 0.001$) [52,54,55].

In a long-term 13-year follow-up study, of six successful recipients of IAT only one developed diabetes with mild fasting hyperglycemia [54]. This finding was consistent with the lowest number of islets this patient received. No other patients required exogenous insulin. Although insulin responses to glucose deteriorated over the course of the study, insulin response to arginine and insulin secretory reserve remained stable for the duration of the study [54]. At the same time, glucose disappearance rates correlated significantly with the number of islets transplanted [54]. Hepatic catheterization studies demonstrated that human intrahepatic islets deliver insulin directly to the hepatic sinusoids; insulin is secreted in a normal pulsatile pattern similarly to the beta cells of native pancreas [56].

UMN, University of Cincinnati, Leicester and other large centers where IAT is performed report that there is a strong correlation between islet yield, insulin independence and graft function. In general, higher yields are associated with better graft function. However, significant overlap does exist. Although many agree that a critical minimal islet cells mass is required to achieve insulin independence, no single islet yield seems to be predictive of the islet function. Bellin *et al.* reported that an islet yield greater than 2000 IE/kg is a good predictor of insulin independence [55]. White *et al.* found that >3000 IE/kg was an important predictor of insulin independence [57]. Sutherland *et al.* observed that 63% of patients who received >5000 IE/kg and without prior pancreatic surgery demonstrated insulin independence at 1-year follow-up, while this number is reduced to 33% in patients with prior surgery [7]. This phenomenon is mostly likely to be related to the ability to obtain better quality and higher quantity of islets from patients in early stages of pancreatic disease. Ahmad *et al.* demonstrated that more than 6635 IE/kg is required to achieve insulin independence in 40% of patients who remained insulin free at 18 months follow-up. He suggested that in order to benefit from IAT, patients with high BMI should lose weight before undergoing surgery [58]. However, this report seems to be controversial as Takita *et al.*, who also investigated the association between islet isolation outcome and BMI in CP patients, reported higher rates of insulin independence in the high BMI group (71%) of patients compared with that in low BMI group (40%), although the difference was not clinically significant [59].

Wahoff *et al.* (1995) reported results from the UMN series of 48 patients who underwent total or near-total pancreatectomy (>95%) and partial pancreatectomy (5%) and IAT [60]. For all, but two patients in this series, the dispersed pancreatic islets were transplanted into the portal vein system. For two patients, islets were transplanted under the kidney capsule, due to portal vein thrombosis in one patient and portal hypertension in the other. Overall, 51% of patients who underwent TP (patients with partial pancreatectomy were excluded from the analysis) were insulin independent 1 month following IAT; 34% remained insulin independent between 2 and 10 years after transplantation without any graft failure at 2 years. Patients with prior surgical procedures had the lowest islet yields with an 18% rate of insulin independence [60]. Not surprisingly, insulin independence after pancreatectomy and IAT strongly correlated with the number of islets transplanted. At the same time, islet yield correlated with previous surgical procedures and the extent of pancreatic fibrosis. Patients with previous resection or drainage procedures had lower islet yields compared with those who had not. Patients with minimal changes in pancreatic parenchyma and minimal fibrosis had higher islet yields that resulted in long-term insulin independence. Additionally, the report indicates that as the degree of fibrosis increased, the probability of high islet yield and insulin independence progressively decreased [60].

Subsequent report from UMN confirmed these results. Patients (n = 409; 53 were children between 5 and 18 years) who underwent pancreatic resection and IAT from 1977 to 2011 were followed. IAT function was achieved in 90% of the patients at 1-year follow-up. At 3 years, 30% of the TP-IAT patients were insulin independent, with another 30% demonstrating partial function. Prior pancreatic surgery and islet yield correlated with the degree of function and insulin independence [52].

University of Cincinnati reported similar results to those reported by UMN. Insulin independence was achieved in 40% of patients with a mean follow-up of 18 months (1–46 months). Factors related to post-operative insulin independence included the number of islet cells transplanted, lower BMI, female gender, lower mean insulin requirement in the first 24 h following surgery and at discharge [58]. A subsequent report from the same center analyzed TP-IAT outcomes in patients diagnosed with genetically-induced CP that underwent TP and IAT, confirming earlier results [61]. Four patients (25%) were reported as insulin independent at 22 months of follow-up. As was the case in other studies discussed here, islet yield was demonstrated to be strongly associated with insulin independence.

A recent study from UMN also evaluated the outcomes of pancreatic resection and IAT in hereditary/genetically linked CP patients. Out of 80 patients followed, >65% were reported to have partial or full β-cell function. When these results were compared with those obtained from patients with nonhereditary CP, patients with genetically linked pancreatitis were younger (22 years old vs 38 years old), had a higher pancreas fibrosis score, longer duration of pancreatitis and trended toward lower islet yield. These results confirmed the fact that TP-IAT is effective in preserving β-cell function in patients with CP due to hereditary cases. However, the authors suggested that TP-IAT should be considered earlier in the course of disease, before pancreatic inflammation results in a higher degree of pancreatic fibrosis and deterioration of islet cells function [62].

In contrast to UMN and University of Cincinnati, patients in the University of Leicester series were treated with TP-IAT for CP, which was related to alcohol in 45% of the patients, and was of idiopathic origin in 40% of the patient cohort. Additionally, there were no correlation between insulin independence and islet yield. It might be associated with the etiology of patients that underwent IAT, as well as patient compliance [63]. Long-term assessment – up to 6 years of follow-up – of 40 recipients demonstrated that 100% of the patients were C-peptide positive; 12 of the patients remained insulin independent, while the other five remained insulin independent with a median of 16.5 months. Although graft function was reported at the time of the follow-up, the level of function seemed to have had deteriorated over time. This was demonstrated by the increased proportion of patients with impaired or diabetic oral glucose tolerance test profile, and by the increase in insulin dose required to maintain blood glucose levels at a normal level. In contrast to UMN reports, islet yield in this group of patients did not seem to correlate with short-and/or long-term graft function. This could be explained by the fact that patient population in the Leicester series was different from that in UMN and University of Cincinnati series. Leicester reported 87.5% of the patients undergoing total or near-total pancreatectomy, compared with 56% in UMN series; and 12.5% of the patients undergoing partial pancreatectomy versus 43% at UMN. Additionally, in the Leicester series 45% of the patients had developed CP because of alcohol intake, compared with 18.75% in the UMN series. Such patients tend to be less motivated to take care of themselves following transplant, that is, they may continue to drink, have poor diet and fail to attend follow-up appointments. All of these factors may lead to poorer blood glucose control by an increased strain on the islets in the immediate post-transplant period. Furthermore, islet isolation technique followed to isolate autologous islets incorporated a purification step, which led to an overall decrease in the number of islet cells harvested. At the same time, when creatinine levels were assessed in this group of patients, no progression suggesting diabetic nephropathy was found [28]. When CP patients treated with TP-IAT (n = 50) were compared with patients undergoing pancreatectomy alone (n = 35), exogenous insulin requirements at 5 years post-transplant were significantly lower in the TP-IAT group compared with the pancreatic resection alone group. Additionally, a number of patients in the TP-IAT group were insulin free [64].

Dunderdale *et al.* assessed the TP-IAT outcomes according to the etiology of CP; out of the 100 CP patients that were followed 30 were diagnosed with alcoholic pancreatitis [65]. The data suggested that patients with alcoholic pancreatitis had lower success rate of islet retrieval, lower islet cell yields and no long-term improvement in patient-reported QOL outcomes, compared with patients with nonalcoholic CP. Based on these observations, the authors suggested that careful evaluation of these patient is warranted before TP-IAT can be undertaken [65].

The islet size distribution was another factor found to be associated with IAT outcome. Patients receiving islet autografts remarkable for their low islet size index were reported to achieve insulin independence at 6 months following IAT. It was postulated that IAT recipients of marginal islet mass grafts could achieve insulin independence provided that smaller islets were transplanted [66]. Furthermore, the use of islet size index and islet dose (expressed as units IEQ/kg) together was associated with the sensitivity of 75% and specificity of 74% in predicting insulin independence.

The timing of the pancreatic resection and IAT has a direct impact on islet yield. A number of studies reported that maximal islet yield and insulin independence may be attained more easily if TP and IAT are performed early in the course of the disease [31,52,58,67–68]. At the same time, Takita showed that good glycemic control could be achieved in patients with both early and advanced stages of the pancreatic disease [59].

IAT in pediatric patients

The prevalence of CP in pediatric populations is not known; what is known is the fact that CP in this patient cohort is rare [69]. The most common etiology of CP in pediatric populations is genetic mutations (PRSS1, SPINK1 and *CTFR*), although childhood CP of idiopathic origin have been reported [70]. Hereditary pancreatitis is most often caused by genetic mutations in the trypsinogen gene (*PRSS1*), which permits unregulated activity of the pancreatic enzyme trypsin within the pancreas, resulting in inflammation and injury. Affected patients present with abdominal pain at a young age (≤10 years) and have a high lifetime risk of exocrine insufficiency and diabetes mellitus. In addition, children with pancreatitis are at risk for the development of pancreatic adenocarcinoma; the incidence of which is increased in this patient population, as well as exocrine and endocrine failure, which is quite common [71]. The course of CP in childhood is similar to that in adults; the disease impairs normal growth and development of child, school attendance, social interactions, and overall child development. Children with CP should be treated to alleviate the abdominal pain, eliminate the needs for narcotic analgesics, preserve β-cell function and improve the QOL [72].

Patients often have pain relief, although pain eventually recurs in up to 50% of patients, and metabolic failure often develops over time. Diabetes is rarely present in children with CP; as for hereditary pancreatitis patients, 5% will develop diabetes by the age of 10 years, usually after the onset of symptoms, while 18% will develop diabetes by the age of 20 years. Appropriate candidates for resection are patients who present with severe and recurring pain, narcotic dependence and/or impaired QOL [70]. The role of surgical management in children with CP is not well clarified; however, different approaches such as partial and total pancreatectomy, as well as Whipple procedure, can be performed [73]. Total pancreatectomy alleviates pain and removes the risk of pancreatic cancer development. For children undergoing pancreatic resection, IAT is considered a viable option to preserve β-cell mass and improve metabolic function. Prior to TP-IAT, islet function is assessed with HbA1c and fasting and stimulated glucose and C-peptide. Lower fasting glucose, lower HbA1c and higher-stimulated C-peptide levels are associated with improved metabolic outcomes [67,70].

IAT procedure in this patient cohort is performed similarly to that in adults. The first reported case of TP in a child was reported in 1989 by UMN, with resulting islet function [59]. Follow-up for this patient was reported at 7 years following transplant; islet function was well-maintained although the patient was not fully insulin independent [10]. To date, TP-IAT procedures has been performed in over 50 children, with the majority of islet grafts infused intraportally [49]. There only one case report of intramuscular islet transplant in a 7-year-old child, with documented graft function and good metabolic control at 2 years after transplant. This patient, however, has never achieved insulin independence. Rafael *et al.* reported outcomes of TP-IAT in children of 18 years of age and younger and found better islet function in the youngest patients [49]. At 1 year after IAT, insulin independence was achieved in 56% of children with another 22% of patients requiring small doses of insulin, and therefore, partial function [49].

Similarly to the results from previous studies in adult patients, children receiving greater number of islets tended to have better islet function [55]. Kobayashi *et al.* demonstrated that longer duration of original disease (>7 years), extensive of fibrosis of the pancreas and severe acinar atrophy have been associated with lower islet yields, higher risk of insulin dependence [31]. However, no specific islet yield was found to predict insulin independence. Graft function in pre-adolescent patients with lower islet yields was better, when compared with adolescent patients with higher islet yields. It is thought that puberty-related insulin resistance might contribute to poor engraftment, decreased graft function and increased loss of islets in adolescent patients [55]. In addition, young children have lower insulin requirements and receive a greater islet number for body weight. Furthermore, as demonstrated in the autopsy studies of the young nondiabetic children, younger patients have higher β-cell replication capacity compared with adult patients [74]. As demonstrated by the histological examination of severely fibrotic pancreatic tissue from three young CP patients, insulin-positive cells were observed within the ductal lumen, thereby providing evidence of islet neogenesis [75]. However, β-cell replication or neogenesis as a result of the co-infusion of ductal tissue with islet cells as part of the IAT has never been demonstrated.

Although alleviation of pain, preservation of β-cell function and good metabolic control are all important outcomes in pediatric patients undergoing TP-IAT, the most critical factor is the dramatic improvement in QOL indicators. According to the literature, self-reported QOL indicators dramatically improve following TP-IAT, which means TP-IAT is associated with not only physical, but also emotional improvement. In the prospective study at UMN, 19 consecutive children, aged 5–18 years of age, were treated with TP-IAT and subsequently completed Medical Outcomes Study 36-item Short Form (SF-36) health questionnaire before and after surgery. Prior to TP-IAT, the children had below average health-related QOL as reported by Medical Outcomes Study SF-36, with the mean physical component score of 30 and a mental component score of 34. At 1 year following surgery, physical and mental components scores were 50 and 46, respectively [10–11,53,76].

In conclusion, approximately 40–50% of children undergoing TP-AIT achieve insulin independence and good metabolic control in the first year after IAT, with the highest rate of insulin independence in preadolescent children [70]. Lower HbA1c, lower fasting blood glucose, and higher basal and stimulated C-peptide are associated with higher islet yields. Although the data in children are not as extensive as adults, a number of studies indicate that younger age at the time of transplant (<13 years), higher islet yield and no history of prior pancreatic surgery are all factors related to successful outcomes [70]. As in adults, a more progressive disease and pancreatic fibrosis in children are associated with lower islet yields and high risk of insulin dependence.

QOL and patient satisfaction

In Western countries, CP is associated with alcohol abuse in approximately 75% of the cases, making it a disease with devastating social consequences since the patients with intractable abdominal pain often become opioid dependent [77]. QOL indicators are measured using health questionnaires which are specifically designed to address specific questions regarding their daily life and how it relates to the disease in question. There are no specific questionnaires for patients with CP; however, some studies have reported the use of health questionnaires directed at the general well-being of the patient. On the basis of the responses obtained, it is possible to evaluate the ability to work, social adaptation, and cognitive factors and emotions that enable the investigator to ascertain the patient's perception of his/her health, that is, the degree of patient's satisfaction with the quality of his/her life.

The main goal of the pancreatic resection with IAT procedure in CP patients is to improve QOL by alleviating intractable pain, elimination of opioid analgesics and preserving β-cell function. Pancreatic resection is a fairly common procedure performed at many centers around the world. Perioperative mortality rates have been reported as 2–6.7% in experienced centers [3]. Berney *et al.* reported that 75% of the CP patients experienced acute episodes of CP 5 months to 13 years prior to pancreatic resection [78]. Following pancreatic resection, however, satisfactory pain control was reported in 90% of the patients [78]. Rodriguez *et al.* demonstrated significant improvement in QOL indicators – as assessed by SF-36 questionnaire – in patients who underwent TP-IAT for the treatment of CP. All patients reported significant preoperative pain, which was treated with opioid analgesics. Following TP-IAT, however, medication was discontinued in 82% of patients [68]. Sutton *et al.* also addressed the issue of QOL indicators in CP patient population and found significant improvement in QOL parameters and pain assessment [60]. Garcea *et al.* evaluated pain relief in patients undergoing TP (±IAT) at 12 months and 5 years after surgery, and detected a decrease in opioid usage from 90.6% to 40.2% and 15.9%, respectively [64].

Because of the long duration of pain in patients with CP, some patients develop a neurological syndrome known as 'central sensitization' resulting in some degree of pain even after TP-IAT [52]. Sutherland *et al.* reported that at 2 years post-transplant, pain control was significantly improved in UMN patients, with SF-36 survey and clinical record review confirming statistically and clinically-significant improvements [52]. The SF-36 survey showed significant improvement in every QOL scale measured following TP-IAT. Despite demographic differences in patient population between UMN and the University of Cincinnati, and University of Leicester, similar results were reported by other all three centers [52]. QOL improved regardless of whether patients achieved insulin independence, although it was greater in the group of patients who were insulin independent, demonstrating the value of preserving the β-cell function. In similar fashion, QOL did not differ significantly between those patients who had or had not waned off narcotic analgesics.

Garcea *et al.* conducted a study to determine the cost–effectiveness of TP with IAT for CP compared with less radical treatments such as medical therapy alone or pancreatic resection. Sixty (n = 60) patients with TP-IAT and 37 patients who underwent TP alone were identified. While TP alone resulted in significant reduction in opioid use, frequency of hospitalizations, lengths of stay and pain assessment, TP-IAT resulted in longer survival than TP alone. In addition, IAT provided insulin independence in 21.6% of patients, while those requiring insulin had significantly reduced their daily insulin requirements compared with TP alone group. Of all patients, 97 (97%) reported that they were pleased with their operation, and >90% of the patients reported that their abdominal pain had disappeared completely. TP-IAT was reported to be cost-effective when compared with nonsurgical therapy, suggesting a survival advantage with TP-IAT approach to treatment of CP [79].

Islet autograft versus islet allograft: comparison of outcomes

Transplantation of allogeneic islet cells as a replacement therapy for patients with poorly controlled T1DM is not a novel idea. It has been pursued since mid-1980. Early attempts to transplant allogeneic islet cells were not very successful. In 1983 the International Pancreas Transplant Registry reported the results of 159 islet cell allografts. Albeit, none resulted in insulin independence that could be associated with the implanted islet graft [80]. At the time, these suboptimal results were thought to be associated with inadequate islet isolation techniques and immunosuppressive regiments utilized at the time. Looking back at the early attempts to isolate pancreatic islet cells, it is now apparent that islet isolation techniques utilized at a time were not particularly optimal for the large-scale isolation of human pancreatic islets [81,82]. Overdigestion of the islet cells was common, and infusion of unpurified or poorly purified Islet allografts were reported to result in portal hypertention and even death [34]. Although none of the Islet allografts results in insulin independence, the data from the clinical trials clearly indicated that allogeneic islet cell transplantation was safe [83].

The data reported to the International Islet Registry in the 1990s demonstrated that 10% of the patients receiving allogeneic islet grafts maintained insulin independence at ≥1-year follow-up. Additionally, a great majority of transplant recipients reported reduced daily insulin intake, improved HbA1c and fewer episodes of hypoglycemic unawareness. This was despite the fact that they continued to require some exogenous insulin [84].

The Edmonton protocol, new immunosuppressive protocols and improved islet isolation methods ushered a new era in allogeneic islet transplantation [85]. The results were encouraging: while the earlier reports identified insulin independence in 10% of the patients and partial graft function in 35% of the patients at 1-year follow-up, the Edmonton group reported a 1-year success rate of 100% in seven islet-alone recipients. However, at 5 years of follow-up graft function and insulin independence was reported in 82 and 7.5% of transplant recipients, respectively [86]. Results from the international multicenter qualifying clinical trial of allogeneic islet transplantation revealed that islet isolation outcome is closely associated with an experienced team of operators. Islet isolation outcomes were not consistent between all centers, with the success rate of islet isolation ranging between 30 and 50% even in experienced centers [87]. This means that four to six donor organs are needed to achieve insulin independence in a single recipient. Inadequate supply of suitable donor organs limits the applicability of allogeneic transplantation to a small cohort of T1DM patients, with other contributing factors being life-long use of immunosuppression regiments and durability of the islet graft. Hence, despite significant improvements in islet isolation outcomes, transplant outcomes and the use of more favorable immunosuppressive regiments, allogeneic islet transplantation remains an experimental procedure applicable to a small cohort of patients with poorly controlled T1DM [88].

On the other hand, autologous islet transplantation after TP for the treatment of CP with intractable abdominal pain has become the standard therapy very early [7]. As already discussed elsewhere in this chapter, TP-IAT effectively reduces abdominal pain by TP, alleviates brittle diabetes by IAT and significantly improves QOL health indicators [4,7,10,11,52,53].

The main difference in transplant outcomes between islet autografts and allografts is the durability of insulin independence. Sutherland *et al.* compared the islet outcomes of 173 patients after pancreatic resection and IAT with that in T1DM islet allograft recipients, the data which were reported by the Collaborative Islet Transplant Registry [7]. The data indicated that 65% of pancreatic resection-IAT patients demonstrated islet cell function within the first year, with 32% of the patients demonstrating insulin independence. At 2 years follow-up, 85% of patients with initial function still had function in contrast to 66% of the patients who received islet allografts. The differences between patients who remained insulin-independent at 2 years follow-up were even greater between two cohorts: of IAT recipients reporting insulin independence 74% remained so, compared with 45% of the islet allograft recipients who became insulin independent after transplant [89]. Bellin *et al.* demonstrated similar islet function – at 2.1 ± 1.2 years follow-up – in islet allotransplant and autotransplant recipients, despite the fact that IAT recipients received less than half of the islet mass compared with allograft recipients [90]. The authors reasoned that better preservation of islet mass in IAT patients was most probably due to the lack of autoimmune destruction of the transplanted islet cells, allogeneic rejection, toxic and diabetogenic effects of immunosuppressive drugs, effects on the donor organ brought about prolonged CIT, and technical factors that influence the outcome of allogeneic islet isolation [90–93]. Among the technical factors that impact the allogeneic islet isolation outcome is the fact that allogeneic islets are obtained from deceased heart-beating donors, and are, therefore, subject to the effects of CIT. Brain death has been demonstrated to closely associate with the upregulation of pro-inflammatory cytokines in the pancreatic parenchyma, and reduced *in vitro* and *in vivo* islet function in a number of animal models [90]. At the same time, prolonged CIT leads to the activation of the inflammatory pathways within the pancreas and results in decreased islet yield and viability, as well as a delay in time to reversal of diabetes in diabetic nude mice [88,94]. Additionally, instant blood-mediated inflammatory reaction (IBMIR) is a nonspecific inflammatory and thrombotic reaction that has been observed at the time of islet infusion in an allograft setting, that is, at the time when allogeneic islets encounter recipient's blood stream [94]. Inflammatory cell infiltration, complement activation and coagulation are the main characteristics of IBMIR, one of main causes of poor engraftment in an allogeneic setting [95].

Despite the absence of aforementioned factors in autograft milieu, there are a number of challenging technical issues that are common to both autograft and allograft setting. First, the islet isolation process common to both auto- and allotransplants strips the islets cells of their native blood supply and induces hypoxia, upregulation of pro-apoptotic factors and β-cell apoptosis [96,97]. Second, on introduction to the intraportal environment, ischemia–reperfusion injury leads to the noted increase in pro-inflammatory cytokines and activation of the complement pathways. These events most likely contribute to the substantial β-cell apoptosis observed in the immediate post-transplant period in both auto- and allo-geneic transplant setting. The occurrence of IBMIR was also addressed in patients undergoing TP-IAT. In patients who received >1000 IE/kg, early damage to transplanted islets was demonstrated by a concomitant rise in thrombin-anti-thrombin-III complex (TAT), C-peptide and pro-inflammatory cytokine levels. Islet viability was significantly decreased [98]. It is safe to assume that protection of islets in the peritransplant period with Withaferin A, an inhibitor of NF-κB, has been demonstrated to alleviate IBMIR *in vitro* – might lead to improved islet engraftment and higher insulin independence rates – in both allo- and auto-transplant setting [99].

Conclusion & future perspective

Pancreatic resection with IAT has been used to treat painful CP for over 30 years. While pancreatic resection alleviates intractable pain and long-term use of narcotic analgesics associated with CP, IAT minimizes the development of surgically induced diabetes by preserving β-cell function. To date, a number of centers and multiple studies have confirmed that pancreatic resection with IAT is safe and efficacious. However, widespread clinical application of IAT is limited to a few centers in the USA and around the world, with the necessary facilities, technology and expertise for a successful islet isolation outcome. Distant islet processing has been proven successful, but very few centers working in the field of IAT have taken advantage of it, despite recent improvements in organ preservation methods that lead to the extended CIT and increased islet yield and viability [100–102].

The efficacy of IAT has been demonstrated by a number of centers, and is manifested by insulin independence and positivity for C-peptide shortly after the transplant, as well as long-term graft function. However, strategies for improvement do exist and should be examined. Improvements to the islet isolation process such as new and improved collagenase and thermolysin/neutral protease solutions, refinements to the purification process, additives utilized during the isolation to protect the islet cells from mechanical and oxidative stress, as well as custom culture media; and islet engraftment process such as protection from innate immunity and inflammation to minimize β-cell apoptosis, and limiting the impact of innate inflammatory or thrombic events on the islet cells in the immediate post-transplant period, are strategies that will likely lead to a larger proportion of insulin-independent patients and improved long-term graft survival.

Additional studies are necessary to investigate the most advantageous implantation site. At the present time, intraportal islet transplantation is a gold standard for islet auto- and allo-transplantation. Although there is paucity of data that clearly demonstrates the safety and efficacy of this site, a number of theoretical drawbacks do exist. These include greater gluco-lypotoxicity exposure, as well as IBMIR reaction demonstrated to take place when islet cells encounter venous blood.

Peritoneal transplants of autologous islet cells have been successfully performed in patients unable to receive all available islets in the liver, and do show comparable results to those obtained with intrahepatic infusion. Future studies are necessary to explore a transplant site that has superior short- and long-term outcomes compared with the liver. In fact, just recently, a Phase I/II clinical trial initiated at our center to explore implantation of allogeneic islet cells in the omentum has been approved by the FDA. The goal is to demonstrate safety and efficacy of the proposed transplant site in the allogeneic model of T1DM.

In conclusion, future advances in islet isolation, wider use of remote islet isolation centers with proven expertise and experience, curtailing the innate immunity- and inflammation-associated damage sustained by the islet graft thereby minimizing β-cell apoptosis, as well as novel implantation site(s) will surely lead to improved short- and long-term IAT outcomes. At the same time, careful evaluation and long-term management of candidate patients by qualified multidisciplinary teams is required and is strongly advised [76].

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