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Short Review

Brief Review: Pancreatic Islet Transplantation for Type 1 Diabetes in Humans

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Abstract

Pancreatic islet transplantation (ITx) has moved from the experimental phase of development to a position of an accepted and appropriate procedure to apply in clinical medicine. The primary indication for use of ITx is for management of dangerous and recurrent hypoglycemia secondary to use of exogenous insulin for management of hyperglycemia in people with type 1 diabetes. ITx involves procurement of a pancreas donated by a person who has died. The organ is taken to a specialized laboratory for isolation of islets that will be infused into the liver via a cannula put into the hepatic portal vein of an awake recipient by a radiologist. Success rates of maintaining normal blood glucose after the ITx are very high and almost as effective as transplanting an entire pancreas via surgery. Often more than one procedure is required to achieve success. One major attraction to the procedure is that it avoids the more dangerous and complicated procedure of surgical transplantation of the entire pancreas. However, in both instances recipients must undergo and maintain immunosuppressive drugs to avoid rejection of the islets. ITx is also used for management of patients with chronic, painful pancreatitis who undergo pancreatectomy. In this instance the patient's own islets are returned by infusion into the liver as is done with type 1 diabetes patients. No

immunosuppression is required. Success rates of autoislet transplantations are also quite high if a sufficient mass of islets can be recovered from the resected pancreas.

Keywords
Islet transplantation; type 1 diabetes

1. Introduction and Objective

The appeal of an islet transplant compared to pancreas transplantation is that the islet procedure is relatively minor with very low risk for complications compared to the major surgery required for a pancreas. The objective of this brief review is to provide an update on the success of islet transplantation and to compare its efficacy and complications with those of pancreas transplantation. In the Collaborative Islet Transplant Registry, which tracks all islet allografts performed in the US and the many of those performed worldwide, 81% of reported transplants were islet transplant alone, 17% islet after kidney, and only 2% simultaneous-islet kidney [1-8]. In the phase 3 multicenter Clinical Islet Transplant-07 trial, which was designed to collect clinical data to support licensure of islets as a cellular therapy in the U.S., adult patients with C-peptide negative type 1 diabetes of ≥5 years duration were considered candidates for islet transplant alone if they had impaired awareness of hypoglycemia or marked glycemic lability, and a history of severe hypoglycemic episodes in the prior year despite optimal medical therapy [2]. For these patients, the risk-benefit ratio of taking immunosuppression is considered reasonable in comparison to the high risks for recurrent life-threatening severe hypoglycemia caused by medical management with insulin. For patients with a prior history of kidney transplant and type 1 diabetes, islet-after-kidney transplant was considered, and were included in the phase 3 multicenter Clinical Islet Transplant-06 trial if patients had impaired hypoglycemia awareness and experienced severe hypoglycemia or they were unable to achieve a hemoglobin A1c <7.5% despite optimal medical management with insulin therapy [9]. For islet-after-kidney, the relative risks associated with islet allotransplant are less as the patient is already receiving immunosuppression and the procedure is minor.

1.1 Procedure and Drugs

Pancreatic islets for transplant are procured from the pancreas of an ABO blood-type compatible deceased donor (Figure 1). Selection of deceased donors for islet transplantation includes consideration of both organ viability and the likelihood that sufficient numbers of islets will be obtained for transplant. Islet allotransplant is conventionally performed only if >4,000-5,000 islet equivalents (IEQ) per kilogram recipient body weight (IEQ/kg) are obtained from the isolation procedure. The islet mass transplanted needs to be sufficient to justify the risk of administering immunosuppression, particularly in islet transplant alone [2, 10]. Islet procurement and isolation is rather complicated and should be attempted only by established centers that specialize in the process. Islets are isolated from donated pancreases by enzymatic and mechanical digestion of the pancreas in a specialized islet isolation laboratory. The pancreatic duct is cannulated, and a collagenase and neutral protease enzyme cocktail is infused intraductally under pressure [11-13]. Following completion of enzymatic distention, the pancreas is mechanically disrupted by use of the

semi-automated method of Ricordi, and the islets are further purified by density centrifugation, targeting a total tissue volume of <7.5-10 mL [11, 14]. The islets are then maintained in a culture media for 36-72 hours while the transplant recipient begins receiving induction of immunosuppression. This culture period may also reduce immunogenicity of the graft by decreasing class I HLA expressing passenger leukocytes, and islet production of chemokines and tissue factor prior to infusion [15-19]. The islets are then infused intraportally into the liver either through direct access of the portal vein via a transhepatic percutaneous approach with interventional radiology guidance, or via infusion in a mesenteric or omental vein accessed by minilaparotomy ([20-23]; Figure 2). Heparin is administered with the islets and subsequently by intravenous infusion to minimize the risk for portal vein thrombosis [24]. After transplantation the patient is switched to subcutaneous administration of heparin for at least the first week post-transplant to prevent microthrombi from affecting islet revascularization. Recipients are placed back on insulin therapy after the procedure, and insulin is weaned as tolerated over the next few months as islets engraft and become more functional [2, 9]. In general, modern immunosuppressive therapy for islet transplant consists of an induction regimen that is given over a short time frame in the peritransplant period, and the maintenance regimen of daily immunosuppression is taken for as long as the transplanted islet continues to function. Administration of any immunosuppression must balance the need to prevent rejection, while at the same time keeping the risks of immunosuppressive toxicities and infection to a minimum [25]. IL2-receptor antagonists (daclizumab and basiliximab) or T-cell depleting agents (anti-thymocyte globulin or alemtuzumab) are given for induction immunosuppression for islet transplants. However, the T-cell depleting agents are largely gaining favor in the most recent era [2, 7, 26-28]. T-cell depletion is advantageous over IL-2 receptor antagonists for protection against acute cellular rejection in islet transplants, and anti-thymocyte globulin may offer additional benefit of relative expansion of the regulatory T-cell pool [29-32]. TNF-alpha inhibition is often co-administered with T-cell depletion in the induction period to protect the intraportally infused islets from the damaging effect of the instant blood mediated inflammatory reaction [31]. Initial maintenance therapy usually includes tacrolimus with either mycophenolate mofetil or sirolimus [1, 2]. Common side effects of immunosuppression include nausea, diarrhea, electrolyte abnormalities, oral ulcerations, hyperlipidemia, cytopenias, and increased serum creatinine. Sirolimus can be associated with painful oral ulcers and many islet transplant recipients initially treated with sirolimus-tacrolimus require transition to a mycophenolate-tacrolimus combination for better tolerance [33]. Major concerns of immunosuppression are the risks of severe or opportunistic infection, nephrotoxicity, and cancers. The risk for skin cancer varies by geographical region and immunosuppression regimen. The use of calcineurin inhibitor therapy (tacrolimus, cyclosporine), alone or in combination with sirolimus, presents risk for nephrotoxicity post-transplant in patients with type 1 diabetes. In islet transplant recipients, low dose tacrolimus + sirolimus maintenance therapy was associated with a ~5 mL/min/year/1.73 m^2 decline in glomerular filtration rate but with significant heterogeneity in among individuals [34]. Sirolimus presents an additional risk of albuminuria, present in about 5% of treated patients [35]172. Careful selection of transplant recipients with normal kidney function before transplant and careful monitoring of renal function and immunosuppression dosing can minimize risk for adverse renal outcomes [36]. Unfortunately, efficient biomarkers for rejection are largely lacking, and because of patchy distribution of islets in the liver, biopsy diagnosis is not

feasible. For islet transplants, acute rejection is often undiagnosed until the recipient presents with sudden onset hyperglycemia, at which point islet damage is likely irreversible.

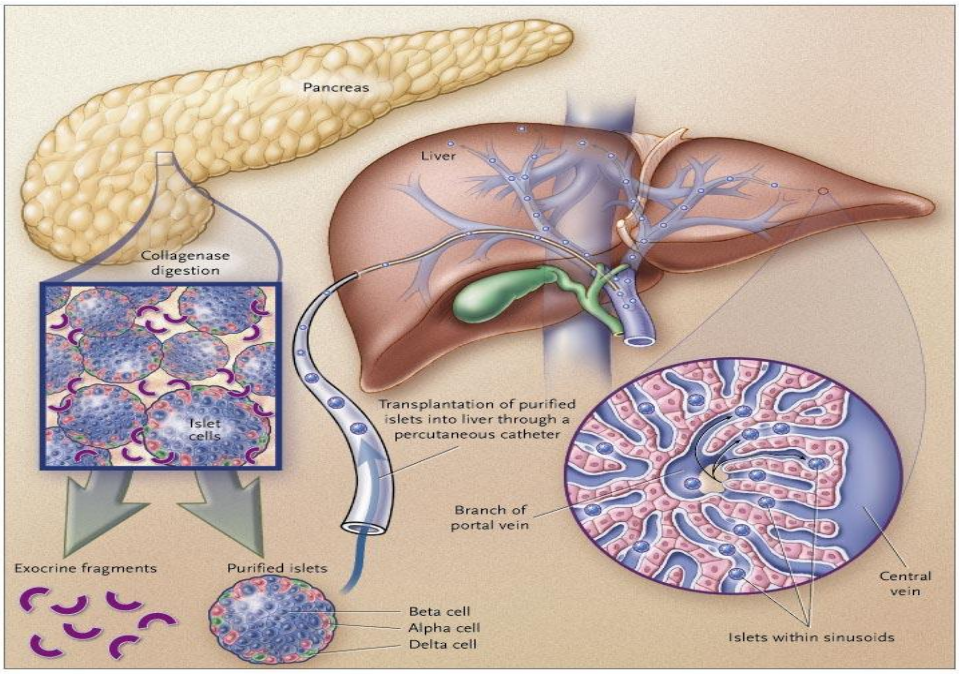

Figure 1 Allogeneic islet transplantation. The procedure involves procurement of a deceased donor pancreas for collagenase digestion and centrifuge purification in a cGMP islet isolation facility. The final islet product may be cultured for up to 72-hours prior to intraportal delivery to the main portal vein using percutaneous, transhepatic access as shown here or via mesenteric vein access achieved by minilaparotomy. Reproduced with permission from Robertson RP. *N Engl J Med* 350: 694-705, 2004 [23].

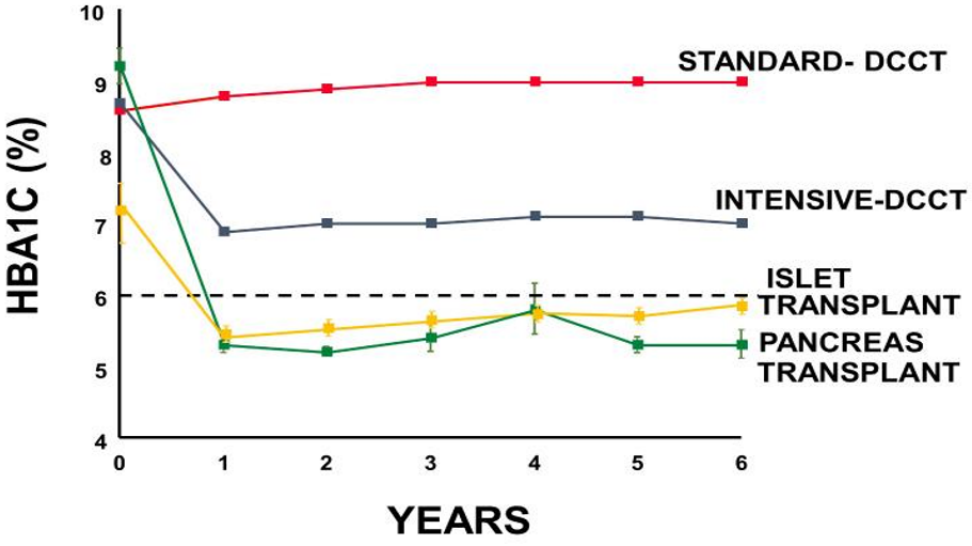

Figure 2 Hemoglobin A1c levels normalize after pancreas (author's data) and islet transplant (updated data from University of Pennsylvania patients receiving islet transplant in the CIT-07 study, [37-46]), contrasted with medical insulin therapy in the Diabetes Control and Complications Trial (DCCT).

1.2 Outcomes

1.2.1 Graft Survival

Islet graft survival is most commonly defined by detectable C-peptide production. Insulin independence and resolution of severe hypoglycemia while meeting hemoglobin A1c targets are common endpoints reported in clinical trials of islet transplantation [2]. Recipients of islet transplants performed in the more recent era were insulin independent in 66% of cases at 1 year, 55% at 2 years, and 44% at 3 years. Nearly 90% were C-peptide positive through 3 years [7]. When current standard immunosuppression regimens were given, including T-cell depleting induction therapy and TNF-alpha inhibition, the 5 year insulin independence rate was 50%, similar to pancreas transplant alone, but less than simultaneous pancreas and kidney [31]. Recipient characteristics may also affect outcomes, with age ≥35 years associated with more favorable outcomes [1]. Additional islets from a second pancreas donor may be required to achieve sufficient islet mass for insulin independence. CIT-07, CIT-06 and the Collaborative Islet Transplant Registry data indicate that 28-46% of islet transplant alone recipients received a single islet graft, while others received two or more infusions to reach reported metabolic outcomes [1, 2, 7, 9].

1.2.2 Patient Survival

Patient survival after alloislet transplant is high. Of 1086 alloislet recipients in the Collaborative Islet Transplant Registry, the mortality rate was 3% over a mean follow up duration of 4.2 ± 3.5 SD years, 57% of which occurred in transplant recipients transplanted in the earliest registry era (1999-2002). Over half of deaths occurred in simultaneous islet-kidney transplant recipients, even though this procedure comprised only 2% of all islet transplants. Islet transplant alone recipients had a 98% patient survival at 5 years post-transplant. This compares to a reported mortality rate of 4% over a mean follow up duration of 2.7 ± 2.8 SD years among individuals with type 1 diabetes referred for islet transplantation who are either found unsuitable for transplant or remained active on the waiting list [37]. Because islet transplant alone is primarily performed to treat type 1 diabetes complicated by hypoglycemia unawareness and recurrent severe hypoglycemic episodes, the primary therapeutic goal of islet transplantation is often to resolve severe hypoglycemia, regardless of whether partial exogenous insulin supplementation is still needed. In the phase 3 CIT-07 trial, the primary endpoint of islet transplant alone was complete resolution of hypoglycemia (days 28-365 post-transplant) with HbA1c <7%, an endpoint that was determined in consultation with the U.S. Food and Drug Administration (FDA). At 1 year, 87.5% met the primary endpoint and at 2 years the median HbA1c was maintained at 5.6% [2]. Secondary analyses from this trial as well as the phase 3 CIT-06 trial further show a benefit to health-related quality of life, particularly reduced diabetes distress scores, reduced fear of hypoglycemia, and improved visual analog quality of life reported on the EQ-5D [9, 38].

The most recent and extensive single-center experience was reported by Marfil-Garza et al. [39] who reported data from studies of 255 islet recipients. Over a median follow-up of 7.4 years, 230 (90%) patients survived. Median graft survival was 5.9 years and 70% of recipients had sustained graft survival. Those with sustained graft survival had longer median type 1 diabetes duration, median older age, and lower insulin requirements. 61% of recipients were insulin-independent at 1 year, 32% at 5 years, 20% 10 years, 11% at 15 years, and 8% at 20 year post-transplant. Multivariate

analyses identified the combined use of anakinra plus etanercept and the BETA-2 score of 15 or higher as factors associated with sustained graft survival. In recipients with sustained graft survival, the incidence of procedural complications was lower whereas the incidence of cancer was higher; most were skin cancers. End stage renal disease and severe infections were similar between sustained and non-susained graft survival groups. In an accompanying report [40], this group of investigators reported that pancreas transplantation showed higher mortality, procedure-related complications, and readmissions compared to islet transplantation. On the other hand, insulin independence, graft survival, and glycemic control were better than in pancreas transplant recipients.

2. Metabolic Outcomes

2.1 Beta Cell Function

Successful alloislet transplantation rivals pancreas transplantation in terms of establishing levels of fasting glucose and HbA1c in the normal or nearly normal range (Figure 2). As opposed to pancreas transplantation in which the organ's venous drainage systemic bypasses first-pass hepatic insulin extraction and results in hyperinsulinemia, the intraportal delivery of transplanted islets for intrahepatic engraftment results in normal hepatic insulin extraction [41] and fasting insulin levels are consequently normal [42]. Like pancreas transplantation, first-phase insulin secretion follows normal secretory dynamics in islet recipients; however, peak insulin secretory responses are often lower than in controls or in recipients of whole pancreas transplant. The lower first-phase insulin secretion in response to glucose is best explained by a reduced islet beta cell mass ultimately surviving engraftment [43]. Consistent with other models of reduced beta cell mass, first-phase insulin secretion in response to arginine is preserved in islet transplant recipients. The reduced functional beta cell mass is most accurately measured from glucose-potentiation of arginine-induced insulin secretion that gives the beta cell secretory capacity. With a decreased beta cell secretory capacity there is a limited insulin secretory reserve such that even insulin independent islet transplant recipients may require temporary periods of exogenous insulin administration during periods of inter-current illness or pregnancy [44] that increase insulin demand. Most importantly, the incidence of severe hypoglycemia and accompanying hypoglycemia unawareness are approximately 90% eliminated. This is explained by appropriate islet cell responses to hypoglycemia with suppression of endogenous insulin secretion. There is the additional benefit of partially increased glucagon secretion, that together with an improvement in adrenomedullary epinephrine secretion, restores the endogenous (primarily hepatic) glucose production response required to defend against the development of low blood glucose [45-48]. This is of utmost importance because frequent hypoglycemia with symptom unawareness is the major clinical indication for alloislet transplantation.

Pancreatic islets are also used for intrahepatic transplantation in patients who have undergone total pancreatectomy for chronic painful pancreatitis. As with alloislet transplantation, successful autoislet transplantation with a sufficient number of islets (approximately 350,000 islets or 5000 islets/kg body wt.) achieves normal or nearly normal levels of fasting blood glucose and HbA1c. However, in the case of autoislet transplantation specifically, a frequent problem following the procedure is hypoglycemia associated with exercise and following high carbohydrate meals [49-51]. This post-transplant complication is thought to be primarily associated with the use of Roux-en-Y

surgery for pancreatectomy. This causes significant alterations in the normal physical relationships between the stomach outlet and the small intestine. This results in a mismatch between glucose and insulin levels such that the autoislets release excessive insulin given the ambient glucose levels in venous blood early after ingestion and insufficient glucagon during the late post-prandial period. Interestingly, the failure of an appropriate glucagon response to insulin-induced hypoglycemia seen with intra-hepatic autoislet transplantation was not observed when a portion of the islets autoislets were transplanted into non-hepatic sites in addition to the usual intra-hepatic site ([51]; Figure 3). This led to the recommendation to consider routinely providing autoislet recipients with intact glucagon responses to hypoglycemia by transplanting at least a portion of the autoislets in a non-hepatic site, such as the omentum [51-53].

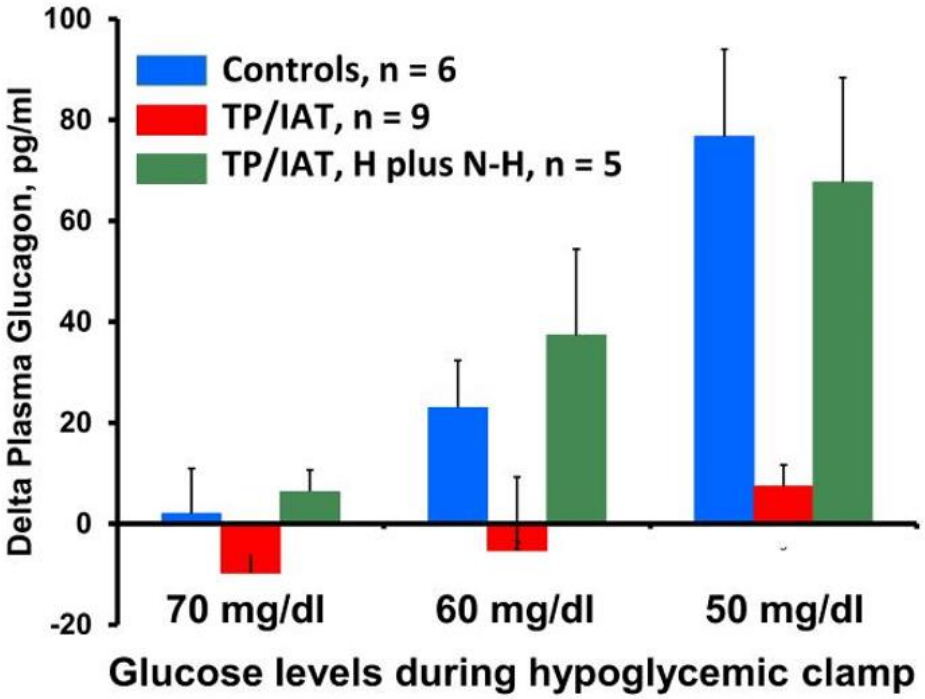

Figure 3 Hypoglycemic clamp studies in patients who underwent TPIAT demonstrated minimal glucagon responsiveness to hypoglycemia with conventional intraportal islet transplant, but restoration of normal glucagon counterregulation when a portion of the islets were transplanted in a non-hepatic site, usually peritoneal cavity. H indicates Hepatic and N-H indicates Non-Hepatic site. Reproduced with permission from Bellin et al, *Am J Transplant.* 2014; 14: 1880-1886 [49].

2.2 Quantification of Transplanted Islets

Metabolic tests have been used to estimate the number of intrahepatic islets that survive intrahepatic transplantation. The test used most frequently involves glucose potentiation of arginine-induced insulin secretion (GPAIS; [52]). Intravenous arginine alone can be used in both diabetic and non-diabetic subjects to induce an acute insulin response. This response is augmented when a prior glucose infusion is used to elevate blood glucose levels. GPAIS has thus been used to estimate insulin secretory reserve and has been applied to recipients of intra-hepatic autoislets. Since these recipients no longer have a native pancreas, insulin responses come exclusively from

their transplanted islets. Correlations between the number of intrahepatic islets transplanted and the magnitude of GPAIS responses are significant. Since the number of islets transplanted is a known value, and the slope of the line reflecting this relationship is close to the theoretical slope observed in normal subjects, this justifies the use of the GPAIS value as an estimate of the number of islets surviving transplantation. Repeated use of GPAIS in the years following islet transplantation may provide a useful estimate of survival of transplanted allo- and autoislets [43].

2.3 Summary and Conclusions

Pancreatic islet transplantation has steadily evolved over the past half century from the status of rare success to that of a predictable degree of success, much as had occurred in earlier years with pancreas transplantation. While the long-term survival rates of the latter still exceed that of the former, the success rates of both appear to be fairly equal when corrected for the durations of time for which each had initially been shown to be clinically successful. Clearly, the major attraction of using islets is the avoidance of the major surgery required of pancreas transplantation and its higher incidence of morbidity and serious surgical complications. Unfortunately, in the United States there remain major regulatory hurdles that limit application of islet transplantation. Nonetheless, successful islet transplantation has provided an important theoretical bridge to the ultimate strategy of using cell-based treatment for diabetes, such as use of stem cells and/or xenogenic porcine islets. That these are important goals is evident by the fact that there are far few fewer human pancreas and islet donors than there are people afflicted with diabetes. This is fortunately not the case for autoislet transplantation as a treatment for chronic, painful pancreatitis because the donor of the islets is the recipient. In this case the main challenge is to perform total pancreatectomy early enough in the course of the disease when there are still a sufficient quantity of viable islets to enable the procedure to provide satisfactory glucose control.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has no conflicts of interest to be reported.

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