

Pancreatic Islet Cell Transplantation in the Treatment of Type 1 Diabetes Mellitus

BY AMISH PARIKH, MD, FRCPC

Pancreatic islet cell transplantation as a treatment modality for type 1 diabetes mellitus (T1 DM) has garnered renewed interest and research over the past few years as a result of advances in the field of transplantation. Worldwide, there are over 40 sites currently developing and implementing this technology. More than 471 patients with T1 DM have received islet cell transplants in the past 5 years.¹ The ultimate goal of islet cell transplantation is to restore normal glucose homeostasis, allow individuals to remain free of exogenous insulin, minimize or eliminate the use of anti-rejection drugs, and eliminate or reverse the microvascular and macrovascular complications of DM. This issue of *Endocrinology Rounds* summarizes the development of islet cell transplantation, outlines the clinical data supporting this technology, and highlights some of the challenges that lay ahead in this new and exciting field.

The first attempt to transplant pancreatic tissue dates back to 1893, in England, when a 15-year-old boy dying of diabetic ketoacidosis had 3 small pieces of freshly slaughtered sheep's pancreas implanted beneath his skin.² Although there was a temporary improvement in urinary glucose excretion before the boy's death 3 days later, this xenograft clearly failed due to a lack of immunosuppression. Subsequently, in 1902, Ssobolew proposed that islet transplantation may be a feasible option,³ but this did not garner much interest until it became apparent that exogenous insulin therapy did not prevent the progression of secondary diabetic complications.

An international registry held in Giessen, Germany, has maintained a comprehensive record of previous clinical attempts at islet transplantation globally (see the Islet Transplant Registry website at www.med.uni-giessen.de/itr/ Accessed Sept. 22 2005). The major problem with earlier attempts at adult islet cell transplantation prior to the 1990s was that <10% of patients were insulin-free at 1-year post-transplantation.⁴ For the most part, these procedures used an anti-rejection regimen consisting of glucocorticoids, anti-lymphocyte globulin, azathioprine, and cyclosporine. Several theories have been proposed to account for why these earlier transplants did not allow patients to reach long-term insulin independence, including:

- inadequate islet cell mass was transplanted
- islets failed to engraft
- islets were damaged by the direct, local toxic effects of immunosuppression.
- ineffective immunosuppression that failed to prevent acute or chronic rejection.⁵

A major breakthrough in islet cell transplantation occurred with the introduction of "The Edmonton Protocol," which is a steroid-free immunosuppressive regimen combined with titrated delivery of an optimal islet mass via a percutaneous trans-hepatic approach into the portal vein. The anti-rejection cocktail consists of daclizumab (a monoclonal antibody against the interleukin-2 receptor), sirolimus, and low-dose tacrolimus. When first published in 2000, the 1-year rate of insulin independence increased to 100% in the 7 patients treated.⁶ As of May 2005, approximately



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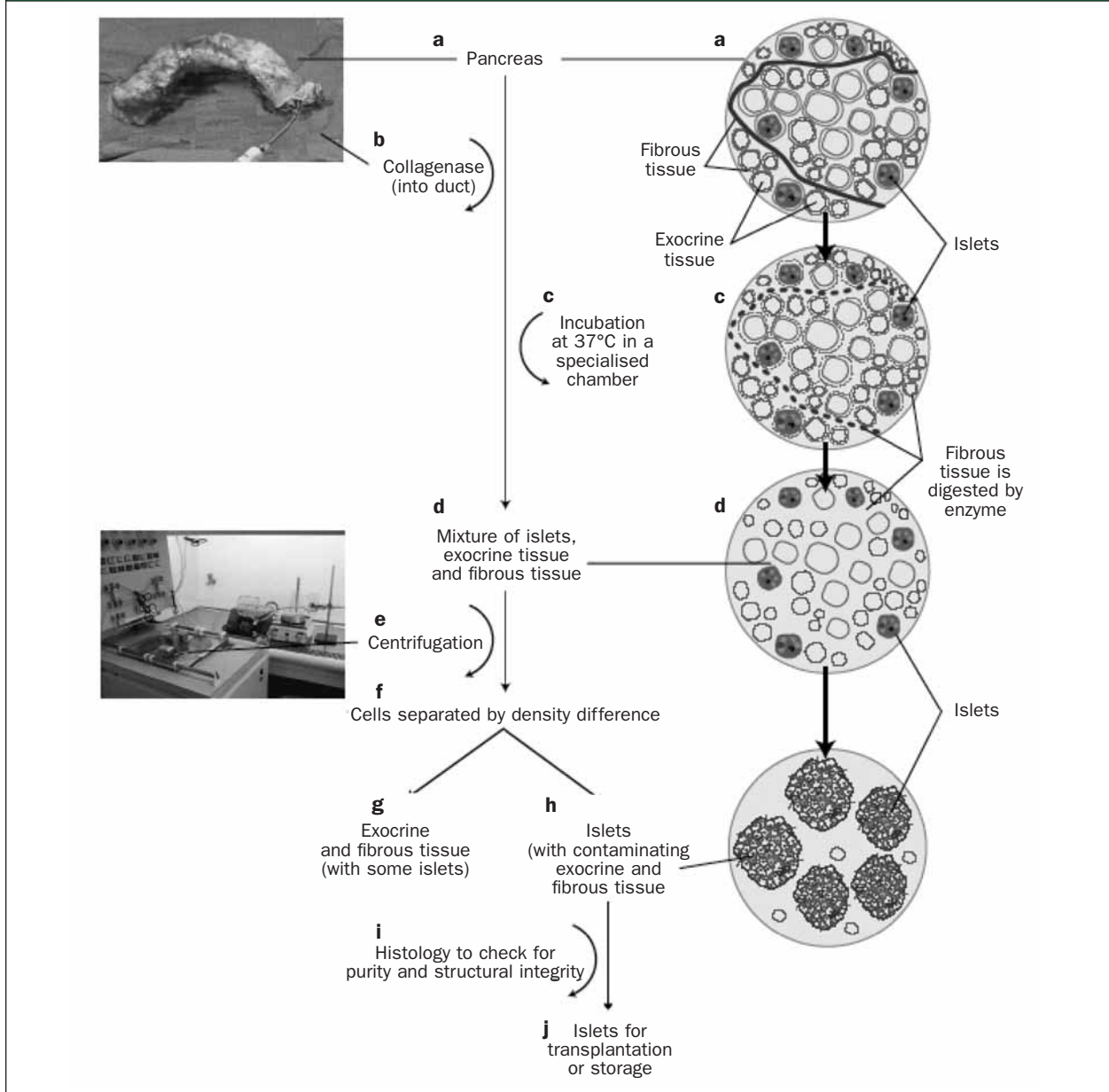
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Figure 1: Procedure for the preparation of isolated human islets¹⁰



76 patients have been treated with the Edmonton Protocol. For completed transplants, approximately 70% are insulin-free at 1 year, but this number is not maintained over time, with insulin independence rates of about 10% at 5 years.⁷ Approximately 80% continue with islet cell function (detectable c-peptide and improved A1c) and relatively stable glycemic control and significantly less severe hypoglycemia. The median duration of insulin independence has been 15 months.

The Edmonton Protocol has been replicated at many centres worldwide and there have been cases where pancreatic islets have been isolated and trans-

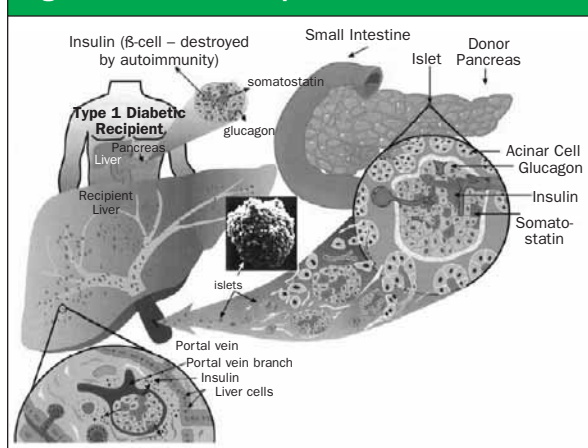
planted in two different cities.^{8,9} The success rate varies, however, from site to site and significantly better results have been obtained at the three most experienced clinical centres, which together reported over 90% of patients achieving insulin-free status. One of the keys to success is the ability to produce high-quality islets for transplantation. Refinements in technique now include the development of reliable single-donor islet transplant protocols whereas, previously, patients treated with the Edmonton Protocol required islets from an average of 2 (and occasionally 3) donors. A general schema for the isolation of islets is shown in Figure 1.¹⁰

Recipient and donor selection

Selection of appropriate donors and recipients is an important aspect of islet cell transplantation. At the present time, the major indications for solitary islet cell transplantation are recurrent severe hypoglycemia and very labile glucose control. In order to better quantify and characterize these problems, Ryan et al¹¹ developed a scoring system for both hypoglycemia and glycemic lability. A composite hypoglycemia score (HYPO score) was devised based on the frequency, severity, and degree of hypoglycemic unawareness. A lability index (LI) was calculated based on the change in glucose levels over time using 4 weeks of glucose records. Finally, a mean amplitude of glycemic excursions (MAGE) was calculated based on 2 consecutive days of 7 readings per day. These scores were determined in 100 randomly selected patients with T1 DM (who were not planning and had not undergone islet cell transplantation) and in patients before and after undergoing islet cell transplantation. Islet cell transplant patients had a mean HYPO score and a mean LI score that was significantly higher than that of the control subjects. The LI correlated much more closely than the MAGE with the clinical assessment of lability. Finally, the mean HYPO score became negligible post-transplantation. Developing a standardized scoring system in this case allows for identification of individuals who are most likely to benefit from islet cell transplantation.

With respect to donor selection, in a retrospective analysis of 326 pancreata, O’Gorman and the Edmonton group¹² derived an algorithm to assess donor quality and pancreas quality to determine the feasibility of a pancreas for islet isolation. As would be expected, there was a strong association between the donor points (score of 0 to 100) and isolation outcome. Factors that were considered when determining the score included donor age, cold ischemia time, body mass index, cause of death, hospital stay, serum amylase or lipase levels, blood glucose, local versus remote organ procurement team, vasopressor levels, and other medical information, including hypertension, alcohol consumption, and smoking history. Factors related to the pancreas itself included quality of procurement, integrity, and quality of packaging, size, fat content, and any damage sustained during procurement or preservation. Developing such a scoring system simplifies the determination of which donors are eligible versus those who are ineligible and also helps predict the potential outcome of islet isolations. This hopefully can help lead to improved clinical outcomes.

Figure 2: Islet cell transplantation¹⁴



Other outcomes

Ensuring proper graft function post-transplant is essential. Ryan et al developed a composite β -score to provide an integrated measure of β -cell function success after transplantation.¹³ Their proposed scoring system gives 2 points each for normal fasting glucose, A1c, stimulated C-peptide, and the absence of insulin or oral hypoglycemic agent use. Therefore, the score ranges from “0” to “8” and correlates well with the glucose value 90 minutes after a standard mixed meal challenge. On follow-up, the β -score rose after the first transplant and was maintained up to 5 years, demonstrating continuing function of the transplanted β -cells. Using this scale, the mean β -score after 5 years of follow up (n = 4 subjects) is 4 out of 8.

Using the Edmonton Protocol, insulin independence post-transplantation has allowed many individuals to restore endogenous insulin production and, therefore, discontinue insulin therapy. The infusion of an adequate islet mass is critical and accomplished by percutaneous transhepatic portal vein transplantation of islets (Figure 2).¹⁴ Insulin independence in these patients has been associated with normalization of A1c and near-perfect glycemic control. However, despite this, hypoglycemic hormonal counterregulation and symptom recognition are not restored by intrahepatic islet transplantation.¹⁵ In particular, glucagon and epinephrine responses and hypoglycemic symptom recognition are not improved. This is in contrast to studies of counterregulation in whole pancreas transplant recipients, which have shown both early and sustained improvements in glucagon and epinephrine responses to hypoglycemia, as well as improvements in symptom recognition of hypoglycemia.¹⁶

However, patients have significantly less fear of hypoglycemia post-islet cell transplantation as com-

pared to pre-transplant and this reduction in fear extends out to 1 and 3 months post-transplant.¹⁷

Complications of islet transplantation have included bleeding related to the percutaneous portal vein access procedure and portal vein thrombosis – both of which are rare. Complications related to antirejection therapy have included hypercholesterolemia requiring statin therapy, severe mouth ulceration, hypertension, and transient elevated liver function tests. There have been no reported cases of post-transplant lymphoproliferative disorders or cytomegalovirus infection or death from the procedure.¹⁸ There are some animal data suggesting that intraportal islets have a potentially negative effect on adjacent liver cells.¹⁹ Whether this translates into any negative clinical consequence in humans is not yet known. There have also been reports by the Edmonton group that successive islet infusions are associated with increased portal pressure when comparing pre-infusion portal pressure with post-infusion portal pressure.²⁰

Research will likely be underway soon to compare long-term outcomes of pancreatic transplantation versus islet cell transplantation. For pancreatic transplantation, there are data to show that a functioning pancreatic graft can prevent diabetic nephropathy and that 5 years of normal pancreatic function can reverse pathological changes of diabetic nephropathy.²¹ Some studies in pancreatic transplantation have also shown improvements in both retinopathy²²⁻²⁴ and neuropathy.²⁵⁻²⁷

Islet cell transplantation in children

There is a worldwide increase in the incidence of T1 DM, especially in young children.²⁸ The management of T1 DM in children is challenging and, given the morbidity associated with its diagnosis in the pediatric population, some have suggested that islet cell transplantation be considered as a treatment modality in children.²⁹ However, several key questions related to transplantation have emerged and include the following:

- Will the initial transplanted islet mass be sufficient over time as the child grows?
- What impact will the islet cell transplant have on long-term quality of life and compliance?
- Will islet cell transplantation succeed in the pediatric population, given the differences in the immune system between children and adults?
- What is the teratogenic potential and the impact on reproductive capabilities?

- Is there a need for lifelong immunosuppression?

Future challenges

Several challenges remain in this new and exciting field of diabetes, the most major and obvious being the small donor pool. It is thought that, currently, islet transplantation can only benefit approximately 0.5% of potential recipients. Countries such as Japan have limited access to cadaveric organ donors.³⁰ Transplantation of pancreatic grafts from living donors is feasible, but has potentially serious complications, including pancreatic fistula, pancreatitis, wound infection, bleeding, and repeat laparotomy.³¹ However, work recently published by Matsumoto³² has shown that transplantation of living-donor islets from the distal pancreas can be sufficient to reverse diabetes and allow for insulin-independence in the recipient. For example, they transplanted living-donor islets from a healthy 56-year-old woman (after distal pancreatectomy) to her 27-year-old daughter with T1 DM and unstable blood sugar control. The transplants functioned immediately and the recipient became insulin-independent 22 days after the operation. However, the long-term outcomes of living-donor islet cell transplantation have not yet been determined.

Advancements in pharmacology are ongoing and focus on minimizing the anti-rejection drugs that patients take and decreasing the risk of subsequent malignancy and infection. New advances in the understanding of the immune system and tolerance will help to also decrease possible rejection (for a recent review, see Goodnow³³). Finally, the search continues for alternative tissue sources that can not only produce insulin, but also are responsive to glucose. Possibilities include human embryonic stem cells, adult stem cells, genetically altered hepatocytes, intestinal mucosal cells, gene therapy, and xenotransplantation. All of these have several technical and ethical hurdles that must be addressed.

In summary, for individuals to be considered for islet cell transplantation, the current indications include both severe hypoglycemic unawareness and very labile blood sugar control, despite an attempted optimization of insulin therapy. Detailed information for patients and healthcare professionals can be found at <http://www.med.ualberta.ca/islet/> (Accessed September 23, 2005.)

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Abstracts of interest

Five-year follow-up after clinical islet transplantation

RYAN EA, PATY BW, SENIOR PA, ET AL.
EDMONTON, ALBERTA

Islet transplantation can restore endogenous beta-cell function to subjects with type 1 diabetes. Sixty-five patients received an islet transplant in Edmonton as of 1 November 2004. Their mean age was 42.9 +/- 1.2 years, their mean duration of diabetes was 27.1 +/- 1.3 years, and 57% were women. The main indication was problematic hypoglycemia. Forty-four patients completed the islet transplant as defined by insulin independence, and three further patients received >16,000 islet equivalents (IE)/kg but remained on insulin and are deemed complete. Those who became insulin independent received a total of 799,912 +/- 30,220 IE (11,910 +/- 469 IE/kg). Five subjects became insulin independent after one transplant. Fifty-two patients had two transplants, and 11 subjects had three transplants. In the completed patients, 5-year follow-up reveals that the majority (approximately 80%) have C-peptide present post-islet transplant, but only a minority (approximately 10%) maintain insulin independence. The median duration of insulin independence was 15 months (interquartile range 6.2-25.5). The HbA(1c) (A1C) level was well controlled in those off insulin (6.4% [6.1-6.7]) and in those back on insulin but C-peptide positive (6.7% [5.9-7.5]) and higher in those who lost all graft function (9.0% [6.7-9.3]) (P < 0.05). Those who resumed insulin therapy did not appear more insulin resistant compared with those off insulin and required half their pretransplant daily dose of insulin but had a lower increment of C-peptide to a standard meal challenge (0.44 +/- 0.06 vs. 0.76 +/- 0.06 nmol/l, P < 0.001). The Hypoglycemic score and lability index both improved significantly posttransplant. In the 128 procedures performed, bleeding occurred in 15 and branch portal vein thrombosis in 5 subjects. Complications of immunosuppressive therapy included mouth ulcers, diarrhea, anemia, and ovarian cysts. Of the 47 completed patients, 4 required retinal laser photocoagulation or vitrectomy and 5 patients with microalbuminuria developed macroproteinuria. The need for multiple antihypertensive medications increased from 6% pretransplant to 42% posttransplant,

while the use of statin therapy increased from 23 to 83% posttransplant. There was no change in the neurothesiometer scores pre- versus posttransplant. In conclusion, islet transplantation can relieve glucose instability and problems with hypoglycemia. C-peptide secretion was maintained in the majority of subjects for up to 5 years, although most reverted to using some insulin. The results, though promising, still point to the need for further progress in the availability of transplantable islets, improving islet engraftment, preserving islet function, and reducing toxic immunosuppression.

Diabetes 2005;54(7):2060.

Beta-score: an assessment of beta-cell function after islet transplantation

RYAN EA, PATY BW, SENIOR PA, LAKEY JR, BIGAM D, SHAPIRO AM. EDMONTON, ALBERTA

OBJECTIVE: Success after islet transplantation can be defined in terms of insulin independence, C-peptide secretion, or glycemic control. These measures are interdependent and all need to be considered in evaluating beta-cell function after islet transplantation. For the current study, a composite beta-score was developed that provides an integrated measure of beta-cell function success after islet transplantation.

RESEARCH DESIGN AND METHODS: The proposed scoring system gave 2 points each for normal fasting glucose, HbA(1c), stimulated C-peptide, and absence of insulin or oral hypoglycemic agent use. No points were awarded if the fasting glucose was in the diabetic range, the HbA(1c) was >6.9%, C-peptide secretion was absent on stimulation, or daily insulin use was in excess of 0.24 units/kg. One point was given for intermediate values. The score ranged from 0 to 8 and was correlated with the glucose value 90 min after a standard mixed meal challenge (n = 218) in 57 subjects before and after islet transplantation. The score was also used to follow subjects for up to 5 years after islet transplantation.

RESULTS: The beta-score correlated well with the plasma glucose level 90 min after a mixed meal challenge (r = -0.849, P < 0.001). On follow-up, the beta-score rose after the first transplant and was maintained up to 5 years, demonstrating continuing function of the transplanted beta-cells.

CONCLUSIONS: The beta-score provides a simple clinical scoring system that encompasses glycemic control, diabetes therapy, and endogenous insulin secretion that correlates well with physiological measures of beta-cell function. On this basis, it is suitable as an overall measure of beta-cell transplant function. The beta-score gives an integrated measure of beta-cell function as a continuum that may be more useful than simply assessing the presence or absence of insulin independence.

Diabetes Care 2005;28(2):343-7.

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