Pancreatic islet transplantation: A review

A new study underway at the UBC Islet Transplant Program may help determine the effect of pancreatic islet cell transplantation on the secondary complications of type 1 diabetes.

The success of pancreatic islet transplantation using the Edmonton protocol is a significant landmark in patient care and research in the search for a cure for type 1 diabetes (T1D). It is estimated that there are approximately 20 to 26 new cases of T1D per 100,000 children aged 0 to 14 years in Canada each year.

The state of complete insulin deficiency seen in T1D is associated with hyperglycemia and long-term secondary complications involving the kidneys, eyes, nerves, and blood vessels. It has been clearly established that tight blood sugar control reduces the likelihood of developing secondary complications from diabetes. Unfortunately, tight blood sugar control with insulin therapy may not prevent all serious complications of diabetes and is associated with increased frequency of hypoglycemia.

Currently, best medical therapy includes more than intensive insulin treatment alone. It includes blood pressure control, blood cholesterol control, and use of protective medications such as angiotensin converting enzyme (ACE) inhibitors. However, even with current best medical therapy, diabetes complications still occur and diabetes has become the leading cause of blindness and kidney disease in adults. The disease often disables people in their middle years and people with diabetes are known to die younger than those not affected.

Pancreatic islet transplantation is a new treatment now being tested as an alternative to conventional medical therapy for T1D. Pancreatic islet cells, which can sense blood sugar levels and release the appropriate amount of insulin, can be transplanted to achieve precise glycemic control. Recent successes reported in some programs have enabled islet transplant recipi-
ments to stop insulin therapy for more than 1 year. This has sparked worldwide interest in the further development and study of islet transplantation to treat diabetes. Although promising, it is not known if islet transplantation is better, safer, or more cost-effective than current best medical therapy for diabetes.

According to the International Islet Transplant Registry, several studies in human islet transplantation were attempted in the 1990s, totaling 47 human islet transplants at 79 institutions worldwide. The majority of these transplants were combined kidney-islet grafts performed with standard combined immunosuppression using anti-thymocyte globulin, glucocorticoids, azathioprine, and cyclosporin. The results of human islet transplant trials prior to 2000 were generally disappointing, with combined 1-year insulin independence rates reported at less than 10%. Fortunately, significant progress has since been made in immunosuppression therapy and islet cell isolation. Using these advances, the Edmonton protocol, published in 2000, showed that islet transplantation was possible for selected patients with labile diabetes using a glucocorticoid-free immunosuppression regimen. The University of Alberta has reported a total of 53 consecutive T1D patients who have received at least one islet transplant as of June 2003. Regarding the three primary indications for islet transplantation, most recipients demonstrated hypoglycemia unawareness (92%), many had lability of blood glucose (51%), and some had progression of secondary complications despite optimal medical therapy (8%). The 1-year rate of sustained insulin independence for all recipients transplanted under the Edmonton protocol has been reported as 80%.

Transplant procedure and issues
Islet tissue for transplantation is procured from cadaveric donors. The technique of islet isolation requires a well-preserved pancreas with a cold preservation time of less than 8 hours, pancreatic duct cannulation and infusion with collagenase, and continuous digestion of the organ in an automated chamber that allows liberation of the islets from the surrounding exocrine tissue. The islets are subjected to in vitro tissue culture for up to 48 hours, thus allowing the transplant to be performed under elective conditions. The patient is admitted the night before the procedure. During the procedure the patient is sedated and the islets are transplanted through the portal vein, which is accessed through a percutaneous transhepatic catheterization procedure undertaken in the radiology department. Post-transplant, patients are observed on an inpatient unit for approximately 24 hours before discharge from hospital, with follow-up in outpatient clinics.

Which groups of patients benefit from transplantation?
Very few patients with T1D can be treated at the current rates of organ donation and islet isolation. As a result, we must be able to identify who will benefit most from this limited resource. The islet transplant program in Edmonton has treated T1D patients with hypoglycemia unawareness, brittle control, and a history of frequent, severe hypoglycemic reactions. In this group, the main benefit identified is the achievement of normoglycemia and consequent improved quality of life. Other groups of patients still need to be identified and studied to determine if and how they benefit from islet transplantation.

What have we learned from whole pancreas transplants?
In patients who have received pancreas transplants, advanced retinopathy does not appear to regress, but the effect on early stages of retinopathy is not currently known. Recurrent nephropathy in transplanted kidneys can be prevented by pancreas transplantation, and reversal of established nephropathy in patients without uremia who received pancreas transplants alone has been observed. Diabetic peripheral neuropathy can be improved, and reduced cardiovascular morbidity and mortality in recipi-
ents of successful kidney-pancreas versus kidney-alone transplants is suggested.13

What are the risks of islet transplantation?
Known risks of islet transplantation from the Edmonton experience include procedural and immunosuppression-related complications. Procedural complications arise from percutaneous transhepatic cannulation of the portal vein with islet cell injection. These complications include pain, bleeding, portal vein thrombosis, and abnormal liver function tests. Immunosuppression-related complications include mouth ulcers, nausea, vomiting, diarrhea, increased creatinine, hypertension, dyslipidemia, acne, oily skin, thin nails, rash, headache, tremor, confusion, myalgia, anemia, leukopenia, thrombocytopenia, vitreous hemorrhage, and arthralgia.5 In addition, long-term risks of transplantation and immunosuppression in general include infection and malignancy.

UBC Islet Transplant Program
The effects of pancreatic islet transplantation on the long-term complications of diabetes are not entirely clear. The UBC islet transplant study is currently recruiting an initial cohort of patients who have some degree of retinopathy and microalbuminuria. Through this study we hope to determine if there is any difference in the progression of microvascular complications whether diabetes patients are managed with the principles of best medical therapy or with islet transplantation.

Based on the Edmonton experience, we expect that a first transplant will decrease a patient’s insulin requirements, either partially or completely. A second or third transplant may be required to receive the number of islets needed to allow insulin independence. Each additional transplant will be similar to the first. The timing of additional transplants will depend on the availability of the donated organs. At this time, a total of 24 islet transplant procedures have been performed in 12 patients.

The outcomes from this study will give us important information on the effectiveness and cost of current best medical care compared with islet transplantation for patients with T1D. Consequently, this study is of significant importance in determining not only the status of our current best medical treatment for diabetes, but in providing a benchmark for assessing the efficacy and safety of new diabetes treatments.

Islet transplant study accepting patients
The UBC islet transplant study is currently accepting patients who meet the following inclusion and exclusion criteria:
• Have type 1 diabetes.
• Have some degree of retinopathy (eye damage).
• Have some protein in the urine.
• Have no heart disease.
• Reside in BC.

In this study we will compare the management of type 1 diabetes in the Islet Transplant Program and the Medical Care Program. The objective of this study is to determine whether there is a difference between programs in preventing diabetes complications. You will be working closely with the diabetes physicians at Vancouver Hospital to manage your diabetes while waiting for a transplant, and with the transplant physicians after you receive an islet transplant. You will also need to be available at very short notice for a transplant.

If you are interested and think that you might qualify:
• Contact (604) 875-5997.
• Fax your most recent eye exam report and urine protein test result to (604) 875-5925 and mark it “Attention Sharon.”
• If you are taking any medication because of protein in your urine, also fax the urine protein test result from the time immediately before you started the medication.

If you are not interested or do not qualify for a transplant but would like to participate in another aspect of this study that measures the needs and health care costs in all people with type 1 diabetes, please contact us.

For more information, phone Ms Sharon Kozak at (604) 875-5997.
The future
The indications for islet transplantation are not generally agreed upon, and it is unclear which patients benefit the most from transplantation. The association of insulin independence with more than one transplant procedure for each recipient remains a major limiting factor. Research is needed to find ways to improve islet yield and islet engraftment, and to develop new immunosuppression regimens that improve islet survival and function.

Limitations in donor supply of islets also remains a barrier to islet transplantation. Estimates suggest there are approximately 400 to 450 cadaveric donors per year in Canada. In future, cell sources such as stem cells may become an alternative to cadaveric sources.

Despite these limitations and uncertainties, continued progress in the area of pancreatic islet transplantation demonstrates the potential of cell replacement therapy for the treatment of diabetes and its secondary complications.

Competing interests
None declared.

References

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