Pancreas Transplantation for Diabetic Patients in Hawaii

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Diabetes mellitus is a common disease affecting a large population in Hawaii. Over the past 20 years, pancreas transplantation has evolved into a viable therapeutic option for selected patients with diabetes mellitus. This report describes the first combined pancreas-kidney transplant performed in Hawaii on June 28, 1993 on a patient with juvenile-onset diabetes mellitus and diabetic nephropathy. The patient has remained off insulin and off dialysis since the transplant. The history, indications, techniques, and potential complications related to this procedure are discussed.

Case 1

The patient was a 38-year old woman from Maui who developed signs and symptoms of diabetes mellitus when she was 5 years old. Insulin was recommended at that time but her family refused. She was started on an oral agent, tolbutamide (Orinase®) in the 1980s. In 1986, she was started on insulin, and prior to surgery was administering 15 units of Humulin in morning and 5 units in the evening. On this schedule, her blood sugar ranged between 70 and 250 mg/dl on any given day. She had no history of seizures, coma or diabetic ketoacidosis, but developed progressive diabetic triopathy, including diabetic nephropathy, retinopathy, and neuropathy. She was started on hemodialysis on July 29, 1991. She had progressive retinopathy and has had bilateral laser photocoagulations as recently as March 1992. She had numbness and parasthesia of both lower extremities secondary to neuropathy; her other medical problems included a left heel ulcer, hypertension, and a history of asthma.

As part of her evaluation for a possible pancreas and kidney transplant, the patient underwent extensive ophthalmologic and cardiac evaluations, including a coronary angiogram; the results were normal. A duplex scan of the lower extremities revealed no evidence of significant atherosclerosis. Her creatinine level was 10.6 mg/dl and her hemoglobin A1C was 12% (normal range is 5.5% to 7.7%). She was deemed to be a good candidate, and was placed on the waiting list for a combined kidney/pancreas transplant on December 1992.

An 18-year old donor, who died of a severe intracerebral injury following a skateboard accident, was pronounced brain dead and consent was given for multiple organ procurement. The donor had a creatinine of 0.8 mg/dl, and normal glucose and amylase levels.

Our patient was hospitalized on the evening of June 27, 1993 and was found to have a serum glucose of 255 mg/dl. She was started on an intravenous insulin drip at 2 units an hour. Her BUN and creatinine levels on admission were 93 mg/dl and 10.6 mg/dl, respectively.

A combined cadaveric kidney and pancreas transplant was performed on June 28, 1993. The operation took approximately 7 hours: A midline incision was made and the kidney was placed intraperitoneally in the left iliac fossa, the renal artery and vein were anastomosed to the patient's left iliac artery and vein, respectively. The kidney graft functioned immediately, producing urine while the patient was still on the operating room table. The pancreas graft was reconstructed on the back table, since the liver was also procured. The donor splenic artery and superior mesenteric artery were reconstructed, using a Y-graft of donor iliac arteries. This Y-graft was then anastomosed to the patient's right common iliac artery; the donor portal vein was anastomosed to the patient's right external iliac vein; a segment of donor duodenum was left intact and was anastomosed to the urinary bladder (Fig 1). The ureter was then anastomosed using the posterior Leadbetter-Politano method.

Postoperatively, the patient was taken to the intensive care unit where she was continued on an insulin drip; her serum glucose had dropped immediately to 86 mg/dl. Intravenous insulin was continued for the first few days in order to maintain tight control of the serum glucose between 100 to 150 mg/dl. The insulin drip was stopped by post-operative day 5 and the patient's blood sugar remained stable while off insulin, ranging between 109 mg/dl to 150 mg/dl. (Fig 2). Immunosuppression was begun with ATGAM® for 10 days, followed prednisone, azathioprine, and cyclosporine A. Antibiotic prophylaxis was given with vancomycin and imipenem (Primaxin®) for 3 days. Fluconazole was given for 14 days, and CMV prophylaxis was instituted with ganciclovir for 10 days, followed by acyclovir for 3 months. The patient was discharged 17 days after the transplant, with a serum

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amylase of 94 IU/l, serum glucose of 110 mg/dl without insulin, and a creatinine of 0.9 mg/dl.

The 6-month follow-up indicates the patient remains off dialysis and insulin. Her most recent serum creatinine was 1.1 mg/dl, and her blood sugar was 96 mg/dl. Her hemoglobin A1C level at 3 months was down to 8.0% (normal 5.5% to 7.7%). The patient did have an episode of acute rejection of both the pancreas and the kidney which was successfully reversed with OKT3®. She had complications related to her steroid immunosuppression, including CMV infection, and a duodenal anastomotic leak, which was successfully repaired. The patient is now at home on Maui.

Discussion

According to the local American Diabetes Association, diabetes mellitus affects about 78,000 residents of Hawaii. Since the discovery of insulin, Type 1 diabetes mellitus has been transformed from a lethal disease to a chronic illness, with many patients going on to develop secondary systemic complications. Since constant euglycemia is unachievable for diabetic patients by any practical mode of exogenous insulin administration, and since hypoglycemia is intolerable, chronic hyperglycemia (as documented by measurements of glycosylated hemoglobin) is the usual state in these patients.[1] After years of debate, the Diabetic Control and Complications Trial (DCCT) has now unequivocally shown that the development of neuropathy and retinopathy is related to the degree to which hyperglycemia is controlled.[2] Complications affecting the eyes, nerves and kidneys are present in more than 50% of patients who survive more than 20 years with diabetes. Even today, the average life span of people with diabetes is significantly shorter than that of the general population.[1]

As the DCCT study indicates,[2] only perfect glucose control for diabetic patients can prevent diabetic complications, but a perfect insulin delivery system has not been developed. An alternative to insulin injection is pancreas transplantation. It was originally thought that since diabetes is caused by insufficient production of insulin by the beta cells in the islets of Langerhans, transplanting these insulin-producing cells would allow perfect control of blood glucose.

The modern history of clinical pancreas transplantation was started on December 16, 1966, when the first human pancreas transplant was performed by Drs Kelly, Lillehei and associates at the University of Minnesota.[1,3] This case involved a uremic diabetic recipient on dialysis who had a simultaneous pancreas-kidney transplant. Since the initial transplant 27 years ago, more than 1,500 pancreases have been transplanted worldwide. The technique has evolved such that the 1-year patient survival is in excess of 90%, and the 1-year pancreas graft survival is approximately 85%.[3] This is comparable to results attained in kidney and other solid organ transplants. Furthermore, successful pancreas transplants have been shown to stabilize or improve neuropathy and prevent recurrence of diabetic nephropathy in kidney grafts.

Diabetes mellitus

Diabetes mellitus (Type 1 and Type 2) affects approximately 5% of the U.S. population. It is the leading cause of blindness each year. Compared with the normal population, patients with diabetes have a 25-fold increase in blindness, a 17-fold increase in risks of renal disease, a 25-fold increase risk of peripheral gangrene and a 2-fold increase in risk of heart disease and strokes[3]. Furthermore, diabetes accounts for 80% of major non-traumatic amputations each year. The late complications of diabetes include macroangiopathy, microangiopathy, retinopathy, nephropathy, cardiomyopathy, and neuropathy. Since the life expectancy of most diabetic patients is shorter than that of the normal population, the goals of the pancreas transplant are: 1) To maintain near normal glucose metabolism; 2) to improve the quality of life for these patients; and 3) to avoid the late complications and higher mortality. In 1990, more than 600 pancreas transplants had been performed worldwide.

Recipient selection

Unlike the heart or liver transplant, which are life-sustaining organs, the pancreas is non-vital in that exocrine and endocrine replacements currently are available. Therefore, the justification of the risk of surgery and life-long immunosuppression cannot be taken lightly. There are 3 categories of patients who could benefit from the pancreas transplant (Table 1).

The first are patients with end-stage diabetic nephropathy who are on dialysis. Many of these patients want to have a kidney transplant for an improved quality of life by being off dialysis. Since they will undergo surgery for the kidney transplant and will require life-long immunosuppression, performing a combined kidney and pancreas transplant in this group would not increase the surgical or immunosuppressive risks significantly. Our patient was in this category. Patients who have had a successful kidney transplant could ask to be candidates for a pancreas transplant, since they are already on life-long immunosuppression. The only disadvantage is that they will have to undergo a second operation for the pancreas transplant.[4,5]

The second category is patients with pre-uremic diabetic nephropathy who have documented macro-albuminuria. The natural history in this group of patients is that they will ultimately require dialysis. Performing the pancreas transplant alone may prevent the diabetic damages to the kidney and ultimately avoid dialysis in these patients.

The final category is patients with severe diabetic management problems. These patients have hyperlabile diabetes or special problems associated with unawareness of hypoglycemia. Some of these patients have a profoundly poor quality of life with seizures and comas, and many of them are afraid to leave their homes. For these patients, a pancreas transplant alone could cure their diabetes and improve their quality of life.[6]

The detailed clinical criteria for candidates for pancreas transplantation or combined kidney/pancreas transplantation are listed in Table 2. Besides active infections or malignancies, other contraindications for pancreas transplantation are listed in Table 3.

Donor selection

Almost all transplant centers now rely exclusively on cadaver donors for their pancreas organs. The cadaveric donor should

Table 1 Possible indications for pancreas transplantation in diabetic patients

Patient's condition	Type of transplantation
End-stage diabetic nephropathy	Combined kidney and pancreas transplant, or pancreas after kidney transplant
Pre-uremic diabetic nephropathy	Pancreas transplant alone
Severe management problems: • Hyperlabile diabetes • Unawareness of hypoglycemia • Severe neuropathic pain	Pancreas transplant alone

Table 2 Clinical criteria for candidates for pancreas transplantation or combined kidney/pancreas transplantation

1. Adults, ages 18 to 50 years
2. Presence of insulin-dependent diabetes
3. Well-controlled blood pressure, with or without medication
4. No evidence of inoperable peripheral vascular disease—specifically, cerebrovascular disease or ischemic ulcers—or previous amputation necessitated by vascular disease
5. Not requiring narcotics or large amounts of analgesics
6. No recent retinal hemorrhage
7. No history of major or significant myocardial infarction
8. No insulin resistance—that is, insulin requirement of no more than 2u/kg.
9. No other contraindications to transplantation, including previous multiple operations, active infections, or malignant lesions
10. Ability to understand risks and benefits of the procedure and to cooperate and comply with the medical program

Table 3 Contraindications for pancreas transplant

- Ongoing peripheral gangrene
- Severe coronary insufficiency with angina or intractable cardiac decompensation
- Severely incapacitating peripheral neuropathy, ie, bedridden patients
- Severely incapacitating autonomic neuropathy, ie, gastroparesis

have no history of diabetes mellitus. Other absolute contraindications include severe chronic pancreatitis and a history of pancreatic damage by trauma. Relative contraindications include alcoholism, recurring acute pancreatitis, and elevated levels of blood glucose or serum amylase levels. The usual criteria for organ donation are noted in this issue in Dr Whitney Limm's article, "The Need for Organ Donation in Hawaii".

Operative technique

The procedure of pancreas transplantation has evolved to the current technique of transplanting the whole pancreas organ with a segment of duodenum for exocrine drainage into the urinary bladder (Fig 1). This approach allows external drainage of the pancreatic duct without the contamination involved with an enteric anastomosis. This also provides the opportunity to monitor urine pH and amylase as a measure of pancreas allograft function and to biopsy the pancreas if necessary via cystoscopy.[7,8]

Immunosuppression, rejection, and complications

The extensive experience at the University of Minnesota has suggested that a triple therapy of maintenance immunosuppression using cyclosporine, azathioprine, and prednisone in combination has the highest success rate. Antilymphocyte globulin, such as ATGAM®, usually is given in the immediate postoperative period.

Rejection of the pancreas allograft is mainly manifested in the deterioration of graft function; inflammatory signs may occur, although inconsistently. A gradual, progressive hyperglycemia with presumed etiology secondary to rejection may be noted. A decrease in urinary amylase output during rejection episodes may occur up to 4 days prior to clinical hyperglycemia. Urinary amylase has proven to be a sensitive indicator of early rejection; early treatment of rejection decreases graft loss. Furthermore, cystoscopically directed biopsy of the pancreas can confirm early rejection. Serum anodol trypsinogen also has been shown to be a marker for early acute rejection. Even with the triple therapy, rejection can occur in 50% to 70% of the cases,[1] as occurred in our patient. Fortunately, rejection can be reversed in over 95% of the cases by using OKT3® a monoclonal antibody directed against T-lymphocytes.

Surgical complications occur in 30% to 40% of cases: hyperamylacemia, graft pancreatitis, pancreatic pseudocysts and ascites, pancreatic fistula, anastomotic leaks with fistula, intra-abdominal abscess, graft thrombosis, bleeding, intestinal obstruction or perforation. Opportunistic infections and potential malignancies also can occur, as in any immunosuppressed patient.

Results

After a successful pancreas transplant, blood glucose normalizes within hours or days. Patients can maintain a normal or near normal fasting blood glucose and half develop normal glycosylated hemoglobin levels. Both were shown in our patient. Most individuals have a normal oral and intravenous glucose tolerance test. A successful pancreas transplant can prevent the occurrence of diabetic nephropathy or the progression of early diabetic lesions in grafts exposed to the diabetic milieu. Depending on the stage of the ophthalmic lesions, the probability of advanced retinopathy progression is not altered in the first few years after a pancreas transplant. However, the

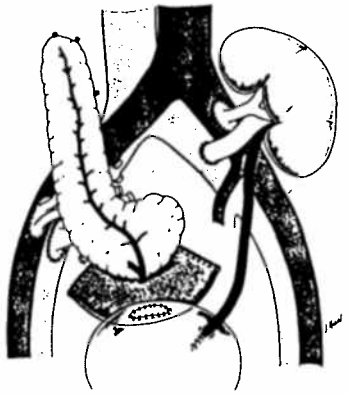

Fig 1.—Technique of combined pancreas-kidney transplantation with the duodenal segment technique. The kidney is placed in the left iliac fossa, and the pancreas in the right. The duodenum is drained into the bladder (Courtesy of WB Saunders Company.)[11]

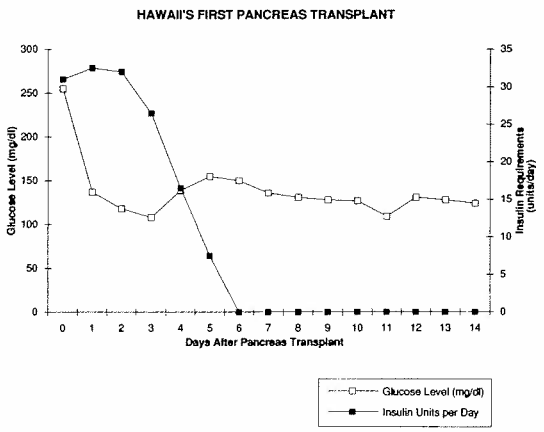

Fig 2.—The glucose level after our patient's successful pancreas transplant. Insulin was stopped after the 5th post-operative day.

retinopathy stabilizes after 3 years with a successful pancreas transplant. Neuropathy improves or stabilizes for most recipients. The nerve conduction velocity and evoked muscle action potentials increase. Patients with severe autonomic neuropathy have a significantly higher probability of survival than patients who did not undergo transplant.

Many studies have looked at the influence of a successful pancreas transplant on the quality of life and the effects of day-to-day living in these patients. The quality of life for many individuals improves simply with insulin independence. Ninety-two percent of patients thought that managing immunosuppression was easier than managing diabetes and insulin.[9] About two-thirds thought that diabetes was more demanding on their families' time and energy than the transplant.[9] All of the patients with successful graft function said they would encourage others with similar diabetic problems to consider a pancreas transplant.[10] Interestingly, even most of the patients with a failed pancreas graft opted for re-transplantation, and most with functioning grafts said that they would undergo a re-transplant if their current graft failed.[10] Since pancreas transplantation is a complicated procedure, it is natural to question whether the benefit is worth the price, and many pancreas transplant recipients have emphatically stated that it is.

The one year pancreas allograft survival rate is over 70% to 85% in diabetic recipients of a simultaneous kidney and pancreas transplant.[3,8] The one-year patient-survival rate is over 90%. This is similar to those achieved with other solid organ transplants.

Summary

Pancreas transplantation as a treatment for diabetes mellitus is the youngest area in the growing field of organ transplantation. Over the past 26 years, it has evolved into a viable therapeutic option for selected patients with diabetes mellitus. Until islet transplant or gene therapy for treatment of diabetes becomes a reality, pancreas transplant remains the only proven cure for selected patients with diabetes mellitus in 1994.

Acknowledgement

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