Recent Advances in Pancreatic Transplantation

Aphrodite Iacovidou, Nadey Hakim

Abstract
Pancreatic transplantation has progressed in the past 25 years since its initial stages, proving to be highly promising for those with diabetes and its resultant multiorgan disorders. Several studies have shown that patients who receive transplants have better glycemic control, blood pressure control, lipid control, and show reversal of microscopic diabetic changes including neuropathy and improved cardiovascular risks. Advances in many fields have made it possible for more than 32,000 procedures to be done worldwide, and 1- and 5-year posttransplant survival to be 95% and 83%. We sought to explore what advances have taken place in surgical techniques, patient selection, and immuno-suppressant therapy to allow this improvement and reduction in complications. New techniques (ie, islet cell implantation) promise early results. However, pancreatic transplant is currently the single existing therapy to establish normal glucose without exogenous insulin.

Key words: Pancreas transplant, Immunosuppression, Survival, Islet cells

In the United Kingdom (UK), 3 million people were diagnosed with either types 1 or 2 diabetes in 2012. By 2025, 5 million people will have the condition. Approximately 10% of this adult population has type 1 diabetes. Diabetes is the most common cause of overt kidney failure having effects on the patient’s daily living and survival. It affects the microvascular and macrovascular systems, causing multiple complications in the cardiovascular, renal, ophthalmic, nervous system, and it reduces survival significantly. Pancreatic transplant can establish normal glucose and glycosylated hemoglobin without exogenous insulin use in insulin-dependent diabetics.

The pancreatic transplant was first introduced by Kelly and associates in 1967, but the procedure did not begin as dramatically as renal transplant, because initially graft and patient survival were poor. A combination of surgical advancements, better immunosuppressive therapy, organ preservation, identifying rejection and treating it appropriately, and early diagnosis of complications have improved donor and graft survival. A recent study by Perosa and associates has shown that there has been an increased number of pancreatic transplants not represented by the numbers given to the International Pancreas Transplant Registry; because there is a lack of standardized methods, protocols, and interpretation of data. In the past 2 decades, 32,000 pancreatic transplants have been done, the majority of which were in the United States, while 6766 were done in Europe, 1945 in Latin America, 22 in Asia, and 5 in Africa. Overall activity is up to 2300 procedures per year.

Currently, there are 3 types of solid pancreatic transplant and pancreatic islet cell transplant used, with the latter being a recent development. These are simultaneous pancreas kidney transplant, pancreas after kidney transplant for those with a renal transplant at an earlier stage for end-stage renal failure, and pancreas transplant alone for those with severe unawareness of hypoglycemic episodes with no renal disease.

Indications for simultaneous kidney and pancreas transplant in the UK have been adapted by the UK Transplant Kidney and Pancreas Advisory Group 2003: type 1 diabetes, or chronic kidney disease...
(either on dialysis or with a dialysis date in the next 6 months). For a pancreas transplant alone, presence of insulin-dependent type 1 diabetes mellitus with significant diabetic complications and life-threatening complications (eg, frequent and severe episodes of hypoglycemia, hypoglycemia unawareness, impaired quality of life, and other severe psychological problems) lead to nonconcordance with insulin therapy. Pancreatic after kidney transplant is indicated for those patients who would qualify for a pancreas alone transplant, those with a previously viable kidney allograft.

Similar to other organ transplants, absolute contraindications to surgery include significant cardiovascular disease (with severe, noncorrectable coronary artery disease, cardiac ejection fraction fraction of less than 50%, recent myocardial infarction, noncurable malignancy, excluding localized skin cancer), active sepsis, active peptic ulcer, severe psychiatric conditions leading to noncompliance, and inability to survive surgery and immunosuppression. Relative contraindications include cerebrovascular event with long-standing impairment; human immunodeficiency virus; hepatitis B and C viruses; a body mass index more than 30; extensive vascular, aortic, and renal artery disease (making surgery high risk); excessive need for insulin greater than 1.5 U/kg/d; and continuous use of alcohol, smoking, and other drugs. Between 2011 and 2012, two hundred thirty-nine transplants took place in the UK. Simultaneous pancreas kidney transplants accounted for most cases (72%), followed by pancreas transplant alone, pancreas after kidney transplant (15%), and islet cell transplant (13%).

As described by David and associates, the traditional procedure involves en bloc dissection of the pancreas and spleen, followed by a splenectomy and a Y vascular anastomosis of the superior mesenteric artery and splenic arteries with the external and internal iliac grafts. The recipient undergoes a laparotomy, and the bladder is exposed if it will be used for drainage. The iliac vessels are divided and prepared, while the graft portal vein anastomosis to the recipient’s right common iliac vein gives systemic release of the endocrine pancreas (insulin, glucagon); the graft portal artery is anastomosed to the right common iliac artery, and the exocrine graft secretions are drained either urinary (latero-lateral bladder-duodenum anastomosis) or enteric (latero-lateral ileum-duodenum anastomosis). This follows hemostasis and closure.

Recent review studies of the 24-year practice in pancreatic surgery have shown improved outcomes and survival, both in the graft and the patient, and better outcomes including reversal of microvascular complications of diabetes (ophthalmic and neurovascular). Patient survival has now reached more than 95% at 1 year after transplant, and more than 83% at 5 years after transplant. The best graft survival is seen in simultaneous pancreas kidney transplant with 86% pancreas and 93% kidney graft function at 1 year. Pancreatic after kidney transplant pancreas graft function reached 80%, and pancreas transplant alone pancreas graft function reached 78% at 1 year. Recent changes in surgical techniques, immunosuppression, and graft preservation account for these improvements in survival and outcomes.

Surgical complications after transplant include thrombosis of graft vessels, bleeding, anastomotic leak (urinary or enteric), graft pancreatitis, pancreaticoenteric fistula, and intra-abdominal sepsis. These have reduced significantly because of new surgical methods, new prophylactic antibiotics and antivirals, more-potent immunosuppressants, and better recipient and donor criteria.

The most common cause of nonimmunologic graft failure is thrombosis with a reported incidence in literature of 10% to 35%. Graft thrombosis always led to the need for pancreatectomy. Over the past decade, new protocols, implementing the use of intravenous heparin and aspirin antiplatelet therapy, have reduced the rate of thrombosis but have increased the rate of bleeding. Postoperative bleeding can be controlled with good hemostasis, and has never led to pancreatectomy, compared with thrombosis.

Follow-up in pancreatic transplant involves regular pancreas biopsies that are the criterion standard, or urinary amylase, if the exocrine pancreas is urinary drained (as traditionally done). Unfortunately, urinary drainage leads to complications after surgery. Loss of sodium bicarbonate secretions of exocrine pancreas in the urine may lead to metabolic acidosis, and in extreme cases, extracellular volume depletion requires hospitalization. Local effects of exocrine secretions include chemical cystitis, urethritis, bladder leak, reflux pancreatitis, recurrent infections, bladder cancer, bladder stones, urethral strictures, urethral
irritation, epididymitis, prostatitis, and prostatic abscess. These complications have been avoided in recent years as more transplant surgeons have chosen enteric drainage of the exocrine pancreas in the duodenal conduit, which was demonstrated in late 1990, with currently more than 80% of procedures being done with enteric drainage. In this procedure, a Roux-Y-limb or a duodenal conduit is used to attach the pancreatic duct. In such cases, graft survival is monitored with pancreatic biopsies or monitoring kidney survival by monitoring renal function in simultaneous pancreas kidney transplant.

Traditional pancreatic transplant has been adapted to consider postoperative complications described with urinary drainage of exocrine pancreas and systemic venous release of endocrine pancreas and subsequent hyperinsulinemia. It has been established that portal graft anastomosis to the recipient portal vein provides better results than does systemic anastomosis. This ensures that the endocrine venous secretions pass through the liver and the portal circulation before the systemic circulation (as described earlier), ensuring better physiologic glycemic control.

A new surgical method for simultaneous kidney pancreas transplant has been implemented in which 2 “hockey-stick” incisions are made either on the lower quadrant, measuring up to 25 cm, 1 to accommodate the kidney on the left side, and the other to accommodate the pancreas and duodenal conduit, allowing 2 surgeons to work simultaneously, as described by Hakim and associates. An extraperitoneal approach is used to reduce bleeding and manipulation of the pancreas, without breaching the peritoneum. Once vascular anastomosis is achieved, the peritoneum is opened on the pancreatic side, and the transplanted duodenum anastomosed to the ileum, ensuring minimal manipulation of the bowel and intra-abdominal contents. This, however, does not allow portal anastomosis of the vessels.

Intra-abdominal infections significantly have been reduced, as new, better antibiotic and antiviral therapies have been introduced and new methods like interventional radiology have been applied in this field, including percutaneous drainage of intra-abdominal abscess, enabling infections to be managed in a nonsurgical fashion, and reducing risks advocated in reopening the peritoneum.

As expected, shorter preservation of the graft offers better results owing to the effect of cold ischemic injury. Because there is a shortage of donors in the UK, it is necessary to use cardiac death grafts that have worse ischemic insult compared with live grafts. To ensure this, more meticulous assessment by the surgeon of the graft, and optimal ischemic time are required to ensure that nonviable grafts are not transplanted.

Immunosuppressant therapy has changed over the years, initially nondepleting antibodies were used, but this has been abandoned with antibody induction therapy taking its place. Between 1980 and 2000, patients received triple immunosuppression with cyclosporine, azathioprine, and prednisone. After 2000, immunosuppression was intensified by induction therapy for both pancreas and kidney transplants with the use of antithymocyte antoglobulin and basiliximab. Azathioprine was substituted by mycophenolate mofetil and cyclosporine by tacrolimus, which have a more-targeted mode of action. Recently, an increasing amount of patients are taking sirolimus alone or in combination. Patients are now rarely discharged on maintenance steroids or azathioprine, because steroid maintenance shows no added advantage to graft survival, while it has many adverse effects.

A recent study by Lindahl and associates, in Norway, showed that simultaneous kidney and pancreatic transplant patients had a better long-term survival from all causes than either live-donor kidney or deceased-donor kidney recipients. Their results are attributed to better glycemic control, better blood pressure and lipid control (which lowers cardiovascular risk), as more than 50% of deaths in this population are attributed to cardiovascular disease. Diabetic nephropathy may improve after normal functioning of the pancreas graft for more than 5 years, while the microscopic changes may be reversed. Initially, diabetic retinopathy worsens because of the alteration in glycemic control, but after 3 years of a functioning pancreas graft, there are fewer complications. Studies also have been reported that show improvement in diabetic neuropathy in both simultaneous pancreas-kidney and kidney alone transplants.

The study performed by Gruessner on 24-year follow-up data from the International Pancreas Transplant Registry investigated the influence of independent risk factors on patient survival and graft
function. It has been shown that patient mortality increased by 3- to 4-fold in patients with failed pancreatic transplant for simultaneous pancreas kidney transplant and pancreas after kidney transplant, 11-fold in pancreatic transplant alone, while independently it increased 17-fold in simultaneous pancreas kidney transplant and pancreas after kidney transplant patients whose kidneys have failed. Mortality also increased in those over 45 years, and in those who had preoperative dialysis. Duct placement had no effect on survival. Using live-donor organs also has improved mortality compared to deceased-donor donations. In terms of graft survival, the highest influence has been shown to be from good immunosuppressant therapy and donor factors. As mentioned earlier, short preservation time is associated with better graft survival, while enteric or bladder drainage shows no effect on graft survival.

Advances in pancreatic transplant have improved patient outcomes, survival, quality of life, and have increased the number of recipients doing well after the transplant, making it more available to older patients with debilitating symptoms. As islet cell transplant is growing and more research studies are coming to light, it may be that these long and complicated procedures may not be necessary in the future, as implanting pancreatic islet cells into the liver may provide sufficient results for patients, while avoiding the complications of solid pancreatic transplant. Implantation is a much simpler method technically than transplant. However, the refinement and isolation of these cells has been particularly challenging but is currently in practice, with studies quoting varying numbers of islets from 300,000 to 750,000 being required to be implanted for 70% of patients to be insulin independent.5

Pancreatic transplant has progressed significantly in the past 25 years, since its initial stages, proving to be a highly promising procedure for patients with diabetes and its resultant multiorgan pathology. Much research has taken place, and collaboration with the use of an international transplant register has made it possible for experiences to be shared and lessons to be learned. It will be exciting to see what another 25 years will bring to this field, and how the lives of these patients can be improved.

References