REVIEW

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Pancreas Transplantation: Past, Present, Future

Shamik Dholakia, MRCS, MBBS, BSc, Shruti Mittal, MRCS, DPhil, MBBS, BSc, Isabel Quiroga, FRCS, DPhil, James Gilbert, FRCS, MA, Edward J. Sharples, FRCP, DPhil, Rutger J. Ploeg, FRCS, PhD, Peter J. Friend, FRCS, MD

Nuffield Department of Surgical Sciences and Oxford Transplant Centre, University of Oxford and Oxford University Hospitals NHS Trust, UK.

ABSTRACT

Diabetes is the pandemic disease of the modern era, with 10% of these patients having type 1 diabetes mellitus. Despite the prevalence, morbidities, and associated financial burden, treatment options have not changed since the introduction of injectable insulin. To date, over 40,000 pancreas transplants have been performed globally. It remains the only known method for restoring glycemic control and thus curing type 1 diabetes mellitus. The aim of this review is to bring pancreatic transplantation out of the specialist realm, informing practitioners about this important procedure, so that they feel better equipped to refer suitable patients for transplantation and manage, counsel, and support when encountering them within their own specialty. This study was a narrative review conducted in October 2015, with OVID interface searching EMBASE and MEDLINE databases, using Timeframe: Inception to October 2015. Articles were assessed for clinical relevance and most up-to-date content, with articles written in English as the only inclusion criterion. Other sources used included conference proceedings/presentations and unpublished data from our institution (Oxford Transplant Centre). Pancreatic transplantation is growing and has quickly become the gold standard of care for patients with type 1 diabetes mellitus and renal failure. Significant improvements in quality of life and life expectancy make pancreatic transplant a viable and economically feasible intervention. It remains the most effective method of establishing and maintaining euglycemia, halting and potentially reversing complications associated with diabetes.

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In 2012 the American Diabetes Association estimated $176 billion in direct medical costs and a further $69 billion due to reduced productivity. Diabetes is associated with multiple systemic complications and reduces survival significantly.[1]

The World Health Organization estimates 9% of the global population, over 600,000,000 people, to be diabetic, with a significant proportion of these patients requiring insulin and approximately 10% of this population having type 1 diabetes.[2] The annual mortality rate of patients with insulin-induced hypoglycemic unawareness is estimated to be between 3% and 6%, making it a significant problem.[3]

The aim of pancreas transplantation is to restore normoglycemia, curing diabetes and limiting the progression of complications associated with diabetes. In the majority of cases, pancreas transplantation is performed in individuals with type 1 diabetes that have end-stage renal disease, usually with uremia, retinopathy, progressive neuropathy, and hypoglycemic unawareness. In those diabetic patients without renal insufficiency, pancreas transplantation alone is performed to prevent life-threatening episodes of deep hypoglycemia, as well as to halt complications.[4]

Pancreas transplantation has not been classed as a lifesaving procedure, unlike other forms of transplantation, but may significantly improve quality of life, providing its recipients with increased independence in all aspects of life.[5] However, not being lifesaving implies that the morbidity and mortality associated with the procedure, including the complications of long-term immunosuppression, must be carefully weighed against any potential benefit.[6]

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Requests for reprints should be addressed to Shamik Dholakia, MRCS, MBBS, BSc, Nuffield Department of Surgical Sciences and Oxford Transplant Centre, University of Oxford and Oxford University Hospitals, NHS Trust, Oxford OX37LE, UK.

E-mail address: sham.dholakia@nhs.net

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Since records began, over 40,000 pancreas transplants have been reported to the International Pancreas Transplant Registry, the majority of them in the US. It is estimated that over 7000 pancreatic transplants have been performed in Europe to date.[7]

The number of patients registered on the active UK transplant list for a pancreas transplant alone (PTA), simultaneous pancreas–kidney (SPK), and islet transplant has increased significantly over the last 10 years, from 132 patients in 2005 to 270 patients in 2014. The number of pancreas donors and transplants has also increased steadily from 118 donors, resulting in 86 transplants in 2004-2005, to 456 donors and 246 transplants in 2013-2014.[5]

CLINICAL SIGNIFICANCE

- The potential to reverse diabetes has to be balanced against the morbidity of long-term immunosuppression associated with transplantation.
- In a patient with renal failure, the treatment of choice is often a simultaneous transplant of the pancreas and kidney (SPK) or pancreas after kidney.
- For a patient with glycemic instability, choices between a solid organ or islet transplant have to be weighed against benefits and risks of remaining on insulin.
- Results of SPK transplantation are comparable with other solid-organ transplants, and there is evidence of improved quality of life and life expectancy.
- There is some evidence of benefit with respect to the progression of secondary diabetic complications in patients with functioning transplants for several years.

TYPES

Currently there are 5 types of endocrine replacement using a donor pancreas and transplantation:

1. Pancreas transplant alone (PTA): Primarily for type 1 diabetics with frequent and severe episodes of hypoglycemia, who may be unaware, have impaired quality of life, or other issues that lead to noncompliance with insulin therapy. These patients tend to have adequate renal function and no uremia. Patients with glomerular filtration rate of 80-100 mL/min/1.73m^2 are unlikely to need a kidney transplant.[8,9]
2. Simultaneous pancreas–kidney transplant (SPK): Both organs come from the same deceased donor. SPK indications have been adapted by the UK Transplant Kidney and Pancreas Advisory Group and include type 1 diabetics with end-stage renal failure requiring dialysis or within 6 months.[10]
3. Pancreas-after-kidney transplant (PAK): Deceased donor pancreas transplantation is performed after a previous, and different, living or deceased donor kidney transplant. PAK transplant is indicated for those patients who would qualify for a PTA, those with a previously viable kidney allograft. The benefits include a reduced waiting time and reduced mortality rate when compared with SPK patients.[11]
4. Simultaneous deceased donor pancreas and live donor kidney transplant has the benefit of lower rate of delayed graft function than SPK and significantly reduced waiting times, resulting in improved outcomes compared with patients waiting for an SPK.[12]
5. Islet cell transplant: despite optimal insulin therapy, a proportion of patients are unable to control their hypoglycemia. It is this group who should be considered for islet cell transplantation. Even in the absence of insulin independence after transplantation, the presence of functioning islets appears to protect against refractory hypoglycemia.[13]

HISTORY

In 1893, an attempt was made to graft 3 pieces of sheep pancreas into the subcutaneous tissue of a diabetic child. Despite initial success, the patient died after 3 days due to severe ketoacidosis.[14] The first human pancreas transplant was performed in December 1966 at the University of Minnesota by the team of Doctors Kelly, Lillehei, Merkel, Idezuki and Goetz, 3 years after the first kidney transplant. A pancreas, along with kidney and donor duodenum, was transplanted into a 28-year-old woman who became insulin independent, but died a short time later due to pulmonary embolism.[15]

Outcomes improved with time, and significantly when simultaneously performing an SPK transplant as the kidney graft functioned as a sentinel for rejection. In PTA, without a kidney, results were significantly inferior as rejection was often missed. Therefore, exocrine drainage managed by way of duodenocystostomy was initially favored so that urinary amylase could be measured as a way of monitoring the pancreas graft in patients, and the introduction of cyclosporin in 1983 significantly reduced rejection rates, improving patient survival.[16,17]

However, the loss of sodium bicarbonate passing out with urine created a metabolic acidosis, and in extreme cases, extracellular volume depletion required hospitalization. Other documented complications include chemical cystitis, urethritis, bladder leak, reflux pancreatitis, recurrent infections, bladder cancer, bladder stones, urethral strictures, urethral irritation, epididymitis, prostatitis, and prostatic abscess.[18,19]

As immunosuppression regimes improved, these complications since have been avoided through a switch back to enteric drainage where the head of the pancreas is joined to the small intestine using a duodenal conduit, which was demonstrated in the late 1990s.[16]