

NEPHROLOGY

Rounds®

Diabetes Mellitus and End-Stage Renal Disease: Current organ replacement options

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Diabetes mellitus represents one of the leading current health concerns, affecting approximately 7.0% of the population in the United States (US). There were 1.5 million new cases of Type 1 diabetes mellitus (T1DM) and Type 2 DM (T2DM) diagnosed in 2005 in patients aged ≥ 20 years. The disease is associated with highly increased morbidity and mortality and is ranked as the seventh leading cause of death in the US. T1DM accounts for 5%-10% of all diagnosed cases of diabetes; of these, 25%-40% will ultimately develop diabetic nephropathy. Transplant options for patients with diabetic nephropathy include kidney transplantation with, or without, whole organ pancreas transplantation. Islet transplants represent an attractive alternative to whole organ pancreas transplantation; however, long-term graft outcomes appear limited at this time. This issue of *Nephrology Rounds* provides an overview of current transplant options for patients with diabetes and end-stage renal disease (ESRD) and compares organ replacement therapies with exogenous insulin therapy.

T1DM affects > 2 million people in the US, with about 30,000 new cases being diagnosed each year. It is the seventh leading cause of death and the leading cause of kidney failure and blindness (in adults aged 20-74 years). In 2002, the total estimated cost of diabetes in the US was 132 billion US\$, with 92 billion in direct medical costs.¹

The Diabetes Control and Complications Trial (DCCT) demonstrated that the risk of complications in diabetes is linked to closely monitored serum glucose concentrations, requiring intensive insulin administration to control blood sugar.² Pancreas transplantation is the only treatment that restores physiological insulin secretion and establishes long-term euglycemia.

Pancreas transplantation

In December 1966, the first pancreas transplant was performed in a uremic patient with T1DM by Kelly and Lillehei at the University of Minnesota.³ Initial results were not encouraging, with 1-year patient and graft survival rates of 67% and 21%, respectively. The success rate improved considerably in the 1980s and, by the 1990s, $> 1,000$ pancreas transplants were being performed annually in the US. As of December 31, 2004, $> 23,000$ pancreas transplants had been reported to the International Pancreas Transplant Registry (IPTR), $> 17,000$ from the US, and almost 6,000 from outside the US.⁴ Patient survival rates at 1 year were $> 95\%$ in each recipient category, with 1-year primary pancreas graft-survival rates of 85% for simultaneous pancreas/kidney transplants and 78% for pancreas after kidney transplants.

Indications

The position statement of the American Diabetes Association (ADA) states "Pancreas transplant should be considered an acceptable therapeutic option to continued insulin therapy in diabetic patients with imminent or established ESRD who have had or plan to have a kidney transplant, since the successful addition of a pancreas does not jeopardize patient survival, may improve kidney survival, and will restore normal glycemia... The pancreas transplant may be done simultaneous to, or subsequent to, a kidney transplant."⁵

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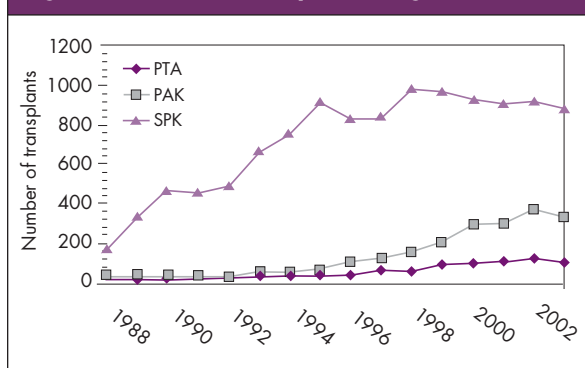
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Figure 1: Pancreas transplant categories



The purpose of pancreas transplantation is to restore endogenous insulin production and render the patient insulin free. A successful pancreas transplant improves quality of life, eliminates acute complications (hypoglycemia/ketoacidosis), and enhances life expectancy. The trade-offs are the operative risk and the risk related to chronic immunosuppression.

Absolute contraindications include active malignancies or infections, major psychiatric illness, medical noncompliance, ongoing substance abuse, and significant irreversible hepatic, pulmonary, or cardiac dysfunction.

Pancreas transplant categories

Pancreas transplant recipients fall into three categories (Figure 1):

- *Simultaneous pancreas and kidney transplant (SPK)*, is usually from the same deceased donor into a patient who has both ESRD and insulin-dependant diabetes.
- *Pancreas after kidney transplant (PAK)*, is performed in a patient who has had his nephropathy corrected by a living or cadaver kidney transplant and is now wait-listed for a pancreas transplant.
- *Pancreas transplant alone (PTA)*, is performed in a patient with normal kidney function. The position statement of the ADA recommends that PTA be considered as therapy only in patients who exhibit a history of frequent, acute, and severe metabolic complications requiring medical attention; clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and a consistent failure of insulin-based management to prevent acute complications.

The majority of the pancreas transplants performed are in the SPK category (67%), followed by PAK (25%), and PTA (8%). In recent years, the majority of patients in the PAK transplant category have received a kidney transplant from a living donor. This proportion increased from 37% in 1988/1989 to 69% in 2002/2003. Most pancreas transplant recipients have T1DM, although 6%-7% are reported to have T2DM.⁴

Although the number of non-Caucasian pancreas transplant recipients is increasing, the majority are Caucasian, with a mean diabetes history of 23-27 years prior to transplantation.

The pancreas donor

Donor selection and organ procurement are vital to the success of pancreas transplantation. Most heart-beating donors, who have been declared brain dead and are under the age of 55, are suitable for pancreas transplantation. The ideal pancreas donor criteria include an age range from 15-40 years with trauma as the cause of death. According to the United Network for Organ Sharing Registry data, the factors associated with an increased risk of graft thrombosis are a donor age > 40 years, cardiovascular (CV) or cerebral vascular accident (CVA) as a cause of brain death, and a pancreas preservation time >24 hours. Visual inspection and palpation of the organ at the time of procurement is critical to success. Other risk factors include prolonged length of hospital stay, multiple blood transfusions, donor body mass index (BMI) >30, weight <30 kg, need for multiple vasopressor agents, alcohol abuse, and prior splenectomy.

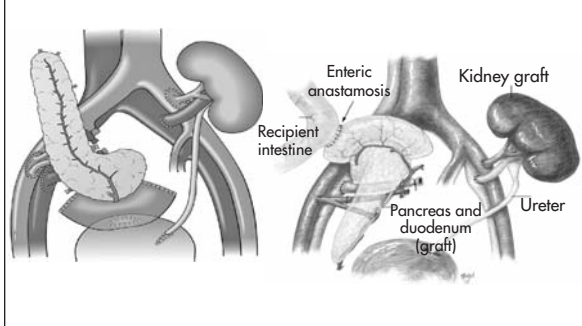
Surgical technique

Surgery is usually performed through a lower midline incision via an intraperitoneal approach. In the case of SPK, the kidney is anastomosed to the left iliac vessels and the pancreas is placed on the right side with the portal vein draining into the right external or common iliac vein (systemic venous drainage). To avoid potential complications of peripheral hyperinsulinemia, portal drainage of the venous effluent has been adopted by some centers. This is a more physiological technique and is also associated with a reduced immune response; however, randomized controlled studies have been unable to show a benefit of portal over systemic venous drainage.⁶ The exocrine secretion of the pancreas can be drained with an enteric (ED) or a bladder (BD) anastomosis (Figure 2).

BD was popular in the 1980s and early 90s, since it is safe, allows measurement of urinary amylase to monitor graft function, and anastomotic complications are easier to manage. However, it is associated with significant metabolic and urological complications as a consequence of obligatory fluid and electrolyte losses. ED is more physiological and avoids metabolic acidosis and urinary complications, but technical failure rates are slightly increased due to anastomotic leaks.

Currently, 70%-80% of all transplants are performed with primary ED. According to IPTR data, patient survival rates are similar for BD and ED cases in all three categories, ranging from 94% to 98% at 1 year.

Figure 2: Bladder-drained pancreas and enteric-drained pancreas



Surgical complications

Surgical complications are seen more commonly with pancreas transplantation compared with kidney transplantation and there is an inherent technical failure rate of 6%-10%.⁷ The majority of complications relate to graft thrombosis, anastomotic leaks after bladder or enteric anastomosis, pancreatitis, and infections. Early thrombosis, within the first 24 to 48 hours, usually due to venous thrombosis of the portal vein, is the most common cause of non-immunological graft loss in the first year. Pancreatitis occurs in 10%-20% of cases and is caused by ischemic damage to the organ during preservation and reperfusion. Management is usually conservative and includes the somatostatin analogue, octreotide.

Immunosuppression for pancreas transplantation

The risk of pancreas allograft rejection is greater than that observed with kidney transplantation and is most likely due to the greater immunogenicity of the pancreaticoduodenal graft. Induction therapy is most commonly applied and its use increased from 64% in 1998 to 80% in 2004. The most common agents for induction are thymoglobulin (44%), alemtuzumab (19%), and the interleukin-2 receptor antibodies, basiliximab or daclizumab (18%).⁸

The majority of recipients (65%) receive the calcineurin inhibitor, tacrolimus, the antiproliferative agent, mycophenolate mofetil, and steroids as maintenance immunosuppression. Only 6% of recipients are on cyclosporine-based immunosuppression and 17% receive the mammalian target of rapamycin (mTOR) inhibitor, rapamycin. The percentage of patients on steroid-free maintenance immunosuppression has increased from 4% in 2000 to 24% in 2004. This increase appears related to the increased use of induction agents such as thymoglobulin and alemtuzumab.

Pancreas allograft rejection

Rejection rates have decreased from 30% in 1998 to <20% in 2005. This observation may be related to modified and more potent immunosuppression. The early clinical presentation of pancreas rejection is different from kidney rejection. Injury to beta cells occurs relatively late and is preceded by acinar injury. Acinar injury causes inflammation and initially presents with pain and discomfort in the area of the graft. This is associated with an elevation in serum amylase and lipase and, if bladder-drained, a reduction in urinary amylase. However, graft pancreatitis can also present in this manner and the "gold standard" for confirming rejection remains a pancreas graft biopsy. A percutaneous approach is the preferred method, using ultrasound or computed tomography (CT) guidance. It is important to remember that rejection, which is diagnosed by hyperglycemia, is a late manifestation and is often irreversible.

In patients with SPK transplants, a renal allograft biopsy can often be used as a surrogate marker to monitor pancreas graft function. In pancreas transplants alone and in cases where the organs are derived from different donors, a pancreas biopsy becomes essential. Ultrasound-guided percutaneous pancreas allograft biopsy has a low rate of complications.^{9,10} Treatment of allograft rejection may require pulse steroids or antibody therapy, and the success rate is high (>90%), if treated promptly.

Effect of pancreas transplantation on the secondary complications of diabetes

A successful pancreas transplant normalizes glucose and hemoglobin A_{1c} levels, and eliminates the need for exogenous insulin. Glucagon recovery in response to insulin-induced hypoglycemia is significantly improved after pancreas transplant compared with non-transplanted diabetic controls. By 3 months post-transplantation, glucagon secretion and hepatic glucose production in response to hypoglycemia also return to normal.¹¹

Diabetic nephropathy

In patients with T1DM and a kidney transplant alone, diabetic nephropathy is characterized by mesangial expansion and a widening of the basement membrane. These changes are evident within a few years post-transplant and, eventually, lead to graft loss within 10-15 years. A successful pancreas transplant prevents glomerular structural changes of the kidney allograft. Diabetic nephropathy has never been reported in a kidney graft when the graft is accompanied by a functioning pancreas graft. In fact, histological

evidence of diabetic nephropathy in native kidneys may resolve between 5 to 10 years after a successful pancreas transplant.¹²⁻¹⁵

Diabetic neuropathy

Peripheral sensory-motor neuropathy is improved after pancreas transplantation and the response lasts as long as pancreas function is maintained.¹⁶⁻¹⁹ Recipients of kidney transplants alone can also improve peripheral neuropathy, but the effect appears more pronounced after a pancreas transplant and the improvement can be observed as late as 10 years after transplant. Autonomic neuropathy takes longer to develop and is much more difficult to measure. Although hypoglycemic unawareness and cardiac autonomic neuropathies appear to improve;^{20,21} overall improvements are modest, at best.

Diabetic retinopathy

Pancreas transplantation does not improve pre-existing retinopathy. In fact, there may be an initial worsening with sudden improvements in blood glucose. However, retinopathy appears to stabilize after 3-4 years and less retinal surgery is required.²²⁻²⁶

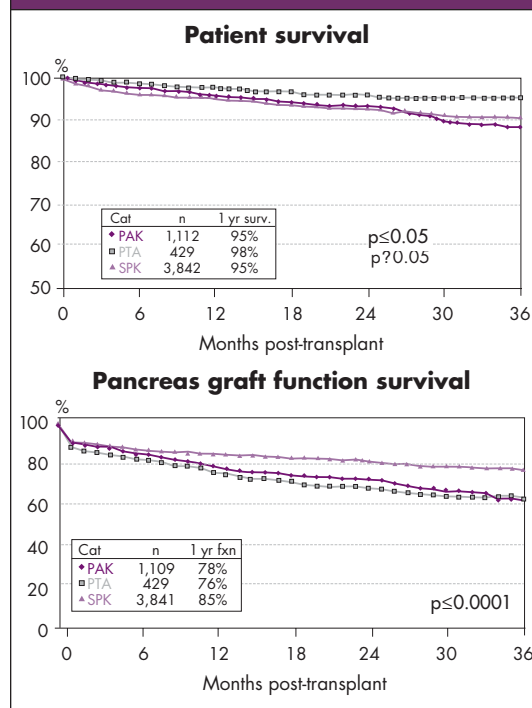
Diabetic CV disease

The most common cause of diabetes-related mortality is associated with CV disease. Diastolic dysfunction, cardiac hypertrophy, as well as vascular endothelial injury, are frequently observed in diabetic patients.^{27,28} Successful pancreas transplantation improves vascular reactivity and diastolic function and slows progression of coronary artery disease. Carotid intima media thickness, a marker for vascular disease risk, improves 2 years after an SPK transplant.²⁹ Despite these improvements, it has been difficult to determine whether peripheral vascular disease improves after transplantation. This is likely related to the advanced stage of these complications at the time of transplantation.

Quality-of-life

Although >40 studies in the recent literature have been reported on quality-of-life after pancreas transplantation, most are retrospective, cross-sectional, and nonrandomized.³⁰⁻³⁶ In spite of these limitations, the majority have demonstrated that quality-of-life is improved by the addition of a pancreas to a kidney transplant. A successful SPK transplant results in improvements in physical function, energy levels, mobility, overall sense of well-being, diabetes-related concerns, and the health impact on the family. Freedom from daily

Figure 3: Outcomes for US deceased donor (DD) primary pancreas transplants by recipient category, 2000-2004 cases⁴



insulin injections and blood glucose monitoring is a significant advantage.

Patient and graft survival

Simultaneous pancreas kidney transplant

Patient survival after SPK transplantation is excellent and has improved steadily since 1995.⁸ Unadjusted patient survival rates at 1 year, 3 years, and 5 years, are 95%, 91%, and 86%, respectively. African-Americans have marginally lower (4%-6%) unadjusted 5-year survival compared with other ethnic groups, with unadjusted kidney graft survival rates at 1 year, 3 years, and 5 years after SPK transplantation at 92%, 85%, and 77%, respectively. The rates are favorable when compared with those observed in patients with diabetes who receive a high-quality kidney transplant alone (89%, 77%, and 65%, respectively). Unadjusted pancreas graft survival rates at 1, 3, and 5 years following SPK transplantation are 86%, 79%, and 71%, respectively.

Pancreas after kidney transplantation

The unadjusted patient survival rates for PAK recipients at 1, 3, and 5 years are 96%, 90%, and 84%, respectively. Unadjusted graft survival rates for PAK at 1, 3, and 5 years are 78%, 66%, and

57%, respectively (Figure 3). The unadjusted 3-year and 5-year graft survival rates have increased by 16% and 4%, respectively, when compared with 1995, indicating long-term benefits.

Should we be performing pancreas transplants?

This central question seems to be clearly answered with a “yes” for SPKs.

A number of studies have examined long-term survival in SPK transplants compared with other forms of therapy for ESRD. Becker and colleagues from the University of Wisconsin demonstrated that diabetic recipients of SPK transplant have an increased observed/expected lifespan compared with recipients of either living donor (LD) or cadaver donor (CAD) kidney transplants alone.³⁷ The annual mortality rate was 1.5% for SPK, 3.7% for LD, and 6.3% for CAD kidney transplant alone recipients. Ojo analyzed data from the US scientific renal transplant registry (SRTR) to determine long-term outcomes in T1DM patients.³⁸ The projected life expectancy was 23.4 years for SPK transplants, 20.9 for LD kidney transplants, 12.6 years for CAD kidney transplants, and 9.4 years for wait-listed diabetic patients.

Demartines³⁹ conducted an evidence-based analysis of SPK and PTA, addressing the question: Is SPK transplant cost-effective? Examining 4 studies that assessed the cost-effectiveness of different treatment strategies for diabetic patients with ESRD, he concluded that SPK transplantation is cost-effective and, together with improved quality of life, superior to alternative treatment strategies such as dialysis, kidney transplant alone, or closely monitored insulin therapy (recommendation grade C).

While the survival benefit for SPK transplants is clear, data with regards to PAK and PTA remain controversial. There seems to be uncertainty in the transplant community about whether solitary transplant (PAK or PTA) provides a survival advantage. Venstrom et al demonstrated a survival disadvantage for PAK or PTA.⁴⁰ These data have recently been challenged by Gruessner et al.⁴¹ This Minnesota group examined the same data and found a modest survival benefit after PAK or PTA. Differences in the determination of waiting-list mortality, specifically in the censoring of waiting-list removals and candidates with renal insufficiency, explain this discrepancy. Nevertheless, even if these points remain contentious, the steady improvement in outcomes from pancreas transplant alone – with excellent 5-year survival rates of >94%

due to recent improvements in surgical care and immunosuppressive treatment – are noteworthy. Thus, the ADA currently recommends both simultaneous and subsequent pancreas transplantation.

Conclusion

Results of pancreas whole-organ transplants have improved steadily and the procedure is currently recommended as the preferred treatment for selected patients with T1DM. Benefits of pancreas transplantation include insulin independence, freedom from the dietary restrictions of diabetes, and a potential improvement in secondary complications. Pancreas transplants should be performed in tertiary care centers with an active kidney transplant program and the expertise to handle the complex medical and surgical issues related to the procedure.

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