Simultaneous pancreas-kidney transplantation: The role in the treatment of type 1 diabetes and end-stage renal disease

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Abstract

Type 1 diabetes mellitus (DM) is one of the most common and debilitating diseases to affect the world. Many patients are afflicted by microvascular and macrovascular complications, and succumb to end-stage renal disease (ESRD). Although dialysis and insulin therapy provides better glycemic control, it nonetheless significantly decreases a patient's quality of life. Moreover, they cannot reverse ESRD or alleviate complications. Simultaneous pancreas-kidney (SPK) transplantation has revolutionized the way we manage type 1 DM; it provides a physiological means of achieving normoglycemia while rendering patients free of dialysis. Understanding this procedure is important because it is becoming a more common management strategy for patients with type 1 DM. In this review, we will begin with a brief summary of type 1 DM, followed by a comprehensive description of SPK procedure, including the history and technique. We will then present the outcomes of transplantation.

Introduction

Type 1 diabetes mellitus (DM) is one of the most common chronic diseases of childhood caused by insulin deficiency secondary to autoimmune destruction of pancreatic beta-cells. The condition affects about 1.4 million individuals in United States, with an annual incidence of 17 cases per 100 000 children.[1] Unmanaged, it can lead to severe long-term complications. These include microvascular events, such as retinopathy, neuropathy and nephropathy, and macrovascular diseases involving cerebrovascular, coronary or peripheral vascular systems.[2,3] These complications are largely attributed to hyperglycemia resulting from poor insulin secretion. Consequently, the mortality rate for type 1 DM is high – 13% after 20 years of disease.[4]

One of the most signification complications of type 1 DM is end-stage renal disease (ESRD).[5] It initially manifests as microalbuminuria with subsequent progression to proteinuria. Without intervention, 80% of these cases lead to nephropathy and ultimately, ESRD (glomerular filtration rate <15 mL/min/1.73 m^2). Eligible patients with ESRD require dialysis or renal transplantation for long-term management.[6]

The Diabetes Control and Complication Trial (DCCT) demonstrated that tight glycemic control, achieved through intensive insulin therapy, slows the progression and reduces the risk of developing micro- and macro-vascular complications.[7] Despite use of insulin pumps and intensive insulin therapy, no exogenous delivery of insulin has been able to sustain normoglycemia as effectively as a functional pancreas. As such, allogeneic pancreas transplantation was developed to achieve normoglycemia and insulin independence. The combination of pancreas and kidney transplantation can render a patient free of both insulin and dialysis with prevention of further diabetic complications, and occasional reversal of established disease.[8]

Pancreas transplantation history

The first pancreas transplantation was performed in 1966 by William Kelly and Richard Lillehei at the University of Minnesota in conjunction with a kidney transplant to treat a diabetic uremic patient.[9] Early procedures were associated with significant morbidity and mortality and performed in low numbers in very select patients. With the advent of cyclosporine and improvements in surgical techniques, 1-year graft survival rates exceeded 70% in 1980s.[10] To date, more than 32 000 cases have been performed worldwide with ever improving outcomes.[11]

Currently, there are 3 methods of solid organ pancreas transplantation. Most (83%) procedures are performed in the context of simultaneous pancreas-kidney (SPK) transplantation where the pancreas is transplanted at the same time as the kidney. The second method is pancreas after kidney (PAK) transplantation (12%) where a pancreas is transplanted to a patient who previously received kidney transplantation. The third method is pancreas transplant alone (PTA)

(5%), which involves transplantation of a solitary pancreas to a diabetic patient with normal renal function. This is performed to counteract life-threatening hypoglycemic unawareness or rapidly progressive diabetic complications refractory to intensive insulin therapy.[12]

Selection process

The SPK procedure is usually reserved for patients with type 1 DM as confirmed by low or absent level of C-peptide.[13] Candidates may also have significant nephropathy or ESRD, along with complications, such as hypoglycemic unawareness, recurrent hospitalization from diabetic ketoacidosis, progressive retinopathy, enteropathy and neuropathy (Table 1).[14]

Table 1. Selection criteria for simultaneous pancreas-kidney transplantation

Confirmed diabetic nephropathy on insulin
Presence of other secondary diabetic complications
Ability to endure surgery and immunosuppression
History of compliance to medical recommendations and therapies
Understanding of potential morbidity and mortality
Creatinine clearance <15 mL/min or on dialysis

Adapted from Sollinger et al.[13]

Surgical procedure

The techniques used for SPK transplantation are diverse and institution-dependent. Most transplant centres use the intraperitoneal approach for graft placement. The pancreas is transplanted to a heterotopic location, usually the right iliac fossa, while the kidney is transplanted to the contralateral iliac fossa. This approach results in fewer peripancreatic fluid collections and wound complications. An alternative approach involves extraperitoneal and ipsilateral placement of both grafts.[15]

Arterial anastomosis may be performed by conjoining the donor superior mesenteric artery and splenic artery to a Y graft of the recipient external or common iliac artery. The donor portal vein is anastomosed to the external iliac vein if systemic drainage is provided. An alternative approach is anastomosis of donor portal vein to superior mesenteric vein if portal venous drainage is available.[16] Although this was performed to reduce lipid dysregulation and rejection rates, contemporary studies have shown very little differences in overall long-term outcomes between systemic and portal drainages.[17]

Outcomes

Survival

It is believed that the SPK procedure prolongs patient survival beyond the survival advantage associated with renal transplantation alone. The 5- and 10-year patient survival rates for SPK transplantation is 87% and 70%, respectively.[18] This is significantly better than the survival rates for patients with type 1 DM receiving maintenance dialysis and who are on transplant waiting list.[19] However, due to inherent biases in listing candidates for transplants and the differences in donor age between SPK and solitary kidney (SK) transplant cohorts, the true survival benefit conferred by the pancreas is unknown.

Graft survival rates are excellent. The pancreatic allograft survival rate is 86% at 1 year and 53 % at 10 years, while kidney survival rate is >95% at 1 year and 60% at 10 years.[18,20] The lower 1-year graft survival rates for the pancreas are secondary to early transplant complications, including thrombosis, pancreatic fistula, and infection.[18,20]

Quality of life

Pancreas transplantation can improve quality of life by eliminating diabetes-associated complications, including hypo/hyperglycemia, metabolic derangements, insulin dependence, glucose monitoring and dietary restrictions.[21] Smith and colleagues compared pre- and post-transplant quality of life and found significant improvement following SPK transplantation.[22] Snort-form-36 Mental Component Summary scores were significantly higher 2 years post-transplant compared to pre-transplant (51.8 vs. 46.8). Similar results were obtained from the Physical Component Summary (PCS) score (48.1 vs. 40.6).[22]

Glycemic control

The vast majority of patients achieve complete insulin independence over the short and long term following solid-organ pancreas transplant. In fact, glycemic control is far superior to that achieved by insulin pump or islet-cell transplants.[23] Mora and colleagues demonstrated that recipients achieved long-term normoglycemic state following SPK transplant.[24] During the 15-year follow-up, HbA1c level remained within the normal range with no significant difference between the first and the last year of follow-up (4.68% vs. 4.76%, $p > 0.05$).[24] Fasting glucose level also remained stable during the same period (3.94 vs. 4.38 mmoL/L, $p > 0.05$).[24] However, oral glucose tolerance test (OGTT) demonstrated decreased pancreatic response, indicating certain deterioration in the functional capability of the allograft over the long term.[24] It is unknown whether this is the effect of immunosuppressive medications (i.e., tacrolimus, sirolimus and prednisone) on islet-cell function, insulin resistance, immune-related chronic changes, or a combination thereof.

Vascular

The pancreas transplant does not reverse established macrovascular disease in recipients. Instead, it is believed to slow down the progression of disease in this high-risk population. Nevertheless, 5 years after transplantation, the prevalence of cerebrovascular disease (CVD), coronary heart disease (CHD) and peripheral vascular disease (PVD) is still 33%, 41% and 41%, respectively. Ten years after transplantations, the risk increased only slightly to 41%, 50% and 50 %, respectively.[25] Using peripheral thermography studies, it is believed that microvascular perfusion is improved post-pancreas transplant as a result of better glycemic control.[26]

Neuropathy

Previous studies demonstrated a benefit of SPK transplant for diabetic polyneuropathy. Kennedy and colleagues analyzed the effect of pancreas transplantation on peripheral motor, sensory and autonomic nerve function based on indexes of nerve conduction velocity and muscle action potential.[27] After 12 months of follow-up, they found a significant improvement in motor and sensory indices. This is supported by Martinenghi and colleagues who found that a sustained normoglycemic state can improve nerve function even if polyneuropathy is advanced.[28]

Nephropathy

Most patients with type 1 DM and ESRD receive SPK to improve their renal function. Fioretto and colleagues reported that 10 years of sustained normoglycemia post-transplant reversed features of diabetic nephropathy.[29] It significantly improved glomerular and tubular lesions, and reduced the thickness of glomerular basement membrane and mesangial matrix. A decrease in urinary albumin excretion rate was also observed (20 mg/day vs. 103 mg/day) highlighting improvement in renal function. However, improvements in diabetic nephropathy post-transplant need to be balanced with nephrotoxicity incurred by the use of immunosuppressive agents, such as tacrolimus and cyclosporine.[30]

Retinopathy

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. Several studies have reported conflicting results about the effects of SPK on retinopathy. However, most recent studies indicate that SPK, with subsequent normalization of blood glucose level, can improve or normalize retinal lesions.[31] Following SPK transplantation, 14% of non-blind eyes showed improvement, 76% remained stable and only 10% progressed further.[32] A separate study reported an improvement in post-transplant visual acuity in 32% of the eyes and frequency/severity of vitreous hemorrhages in 46% of eyes.[31] It may take up to 4 years before noticeable functional improvement in retinopathy and acuity may be observed. Pancreas transplantation, however, cannot reverse established visual loss.

Conclusion

SPK transplantation is the most effective treatment for patients with type 1 DM and ESRD. It addresses renal failure and provides physiological means of attaining stable insulin secretion. Although it involves major surgery and is not without risks, SPK transplantation nonetheless increases patient survival, enhances quality of life and prevents progression of diabetic complications. As such, SPK transplantation should be considered in all eligible patients.

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