Kidney Allograft Outcome in Simultaneous Pancreas-Kidney Transplantation

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Abstract

Background: In simultaneous pancreas-kidney transplantation, with both organs coming from the same donor, the addition of a pancreas to the kidney transplant does not jeopardize the kidney allograft outcome despite higher postoperative SPK morbidity. Pancreas allograft outcome has recently improved due to better organ selection and more accurate surgical techniques.

Objective: To demonstrate the positive impact of SPK on kidney allograft outcome versus kidney transplantation alone in insulin-dependent diabetes mellitus patients with end-stage renal failure.

Methods: We performed 39 consecutive SPKs in 14 female and 25 male IDDM patients with renal failure after an average waiting time of 9 months. Multi-organ donor age was 30 years (range 12–53). The kidneys were transplanted in the left retroperitoneal iliac fossa following completion of the pancreas transplantation; kidney cold ischemia time was 16±4 hours. Induction anti-rejection therapy was achieved with polyclonal antithymocytic globulin and methylprednisolone, and maintenance immunosuppression by triple drug therapy (prednisone, cyclosporine or tacrolimus, and azathioprine or mycophenolate mofetil). Infection and rejection were closely monitored.

Results: All kidney allografts produced immediate urinary output following SPK. Two renal grafts had mild function impairment due to acute tubular damage but recovered after a short delay. Three patients died from myocardial infarction, cerebrovascular event and abdominal sepsis on days 1, 32 and 45 respectively (1 year patient survival 92%). An additional kidney allograft was lost due to a renal artery pseudo-aneurysm requiring nephrectomy on day 26. Nineteen patients (49%) had an early rejection of the kidney that was resistant to pulse-steroid therapy in 6. No kidney graft was lost due to rejection. Patients with acute kidney-pancreas rejection episodes suffered from severe infection, which was the main cause of morbidity with a 55% re-admission rate. Complications of the pancreas allograft included graft pancreatitis and sepsis, leading to a poor kidney outcome with sub-optimal kidney function at 1 year. Kidney graft survival at one year was 89% or 95% after censoring the data for patients who died with functioning grafts.

Conclusions: Eligible IDDM patients with advanced diabetic nephropathy should choose SPK over kidney transplantation alone from either a cadaver or a living source.

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Selected IDDM patients with end-stage diabetic nephropathy who are eligible for kidney replacement therapy may choose between kidney transplantation and simultaneous pancreas-kidney transplantation. In many countries plagued by organ shortage, living-related donation is an acceptable practice. In Israel, most patients with end-stage renal disease who have the possibility of choosing a living donor will tend to pursue this option. Besides its obvious advantages of time scheduling, living donor kidney transplantation also results in better short and long-term kidney outcome than cadaver kidney transplantation [1]. Thus, until recently, when a donor was available IDDM patients considering SPK were encouraged to undergo living-related kidney transplantation instead, because renal allograft survival was superior and less immunosuppression was required [2].

Lately however, improved organ selection, better pre-transplantation treatment and accurate surgical techniques have enhanced pancreas transplant outcome [3]. The addition of pancreas transplantation to kidney transplantation, with both organs from the same donor, does not jeopardize the kidney allograft outcome despite higher postoperative SPK morbidity [4,5]. Moreover, reduced cold ischemia time, careful selection of pancreas-kidney donation, and close monitoring of both grafts during the course of SPK have further improved the kidney outcome [6]. In fact, the long-term results achieved for kidneys in SPK are now better than for cadaver kidney grafts [7].

SPK = simultaneous pancreas-kidney transplantation
IDDM = insulin-dependent diabetes mellitus

We suggest that the positive impact of SPK on patient and kidney allograft outcome may further influence both IDDM patients with advanced diabetic nephropathy and their physicians towards choosing SPK over kidney transplantation alone, from either a cadaver or a living source.

Materials and Methods

During a 10 year period we performed SPK in 39 consecutive selected IDDM patients (14 females and 25 males) with end-stage diabetic nephropathy. The waiting time prior to transplantation was 9 months (range 3–22). Pancreases and kidneys were procured from young brain-dead cadavers (12–53 years old) from which other organs were also obtained. Most of the kidneys (97%) were transplanted in the left retroperitoneal iliac fossa following completion of the pancreas transplantation. Kidneys were revascularized after a cold ischemia time interval of 16±4 hours. Induction anti-rejection therapy was achieved with intravenous polyclonal anti-T lymphocyte globulin ATG-F®(3 mg/kg/day for 4 days) and methylprednisolone (500 mg). Rejection prophylaxis was maintained with the combination of prednisone (100 mg/day tapered to 15 mg/day by 1 month), cyclosporine (8 mg/kg/day adjusted to keep whole blood levels at 150–200 ng/dl) or tacrolimus (0.2 mg/kg/day adjusted to 10–15 ng/dl levels), and azathioprine (2 mg/kg/day) replaced recently by mycophenolate mofetil (2 mg/day). The indication for renal allograft biopsy was a rising serum creatinine or a suspected pancreatic rejection.

The impact of pancreas transplant complications, rejection and infection on the kidney transplant outcome of our SPK series was analyzed and compared to the outcome of living [8] and cadaver kidney transplants in age-matched type 1 diabetes patients reported in the Clinical Transplant series [9].

Results

All kidney grafts produced immediate urinary output following revascularization. Acute tubular damage related to preservation injury occurred in two renal grafts that resumed normal function after a short delay.

Biopsy-proven rejection of kidney grafts occurred in 19 patients (49%), 6 of whom required additional anti-lymphocyte antibodies to reverse steroid-resistant events. Over the past 2 years the rate of early rejection events has decreased (30%).

During the first postoperative year, infection – which was defined as any clinical event and/or positive cultures except for asymptomatic bacteriuria – occurred in 31 patients (78%) and was the main cause of morbidity. All patients with acute pancreas-kidney rejection experienced severe infection.

Graft-related complications, together with inherent complications of diabetes (19%), resulted in a re-operation rate of 60%, re-hospitalization rate of 55%, and a mean total one year hospital stay of 42 days. Among pancreas allograft-related complications, graft pancreatitis and intraabdominal sepsis were associated with alteration of the kidney allograft function, as manifested by serum creatinine levels of 1.7 mg/dl at one year in SPK compared to 1.4 mg/dl in the reported kidney transplants.

Three patients died from myocardial infarction, intra-abdominal sepsis following a pancreas allograft leak and cerebrovascular event on days 1, 32 and 45 respectively. The causes of kidney allograft failure were patient death (in three with graft function) and renal artery pseudo-aneurysm requiring nephrectomy on day 26. Finally, one year patient survival was 92%. At one year, kidney graft survival was 89% or 95% after the censoring of data for patients who died with functioning grafts.

An analysis of United Network for Organ Sharing data encompassed more than 2,200 kidney transplants alone [9]; the figures were 93% and 88% for patient and graft survival respectively. In the report from Wisconsin University [8], only recipients of an HLA-identical sibling kidney had survival rates as high as their selected SPK recipients, 98% and 94% respectively.

Discussion

IDDM patients with advanced diabetic nephropathy who are eligible for transplantation are informed about the shortage of cadaver organs and the mean expected waiting time before one becomes available. The choice between kidney alone or SPK will be influenced, among other factors, by the patients' quality of life while on dialysis, their understanding of the ongoing deterioration secondary to diabetes, and their reluctance to accept the high morbidity rate inherent with pancreas transplantation. Few patients will opt for a cadaver kidney alone rather than SPK, since the long waiting time for cadaver kidneys in Israel (3 years 8 months) is detrimental. In addition, the long-term results achieved for kidney grafts in SPK are better than for cadaver kidney grafts [7]. However, when a living donation is an option, few patients will decline the offer to forego dialysis.

Our retrospective study emphasizes the overall superior results of kidney outcome in SPK versus observed actual results in kidney-alone transplantation. There is some concern that mid-term function of the kidney graft in SPK is sub-optimal at one year, but in the long term this is corrected and is better than for kidney graft alone.

Despite poor HLA match, severe macrovascular changes and severe fluid imbalance following pancreas transplantation, the immediate results of the kidney transplant in SPK are excellent due to organ quality, the young age of donors, short ischemia time, experienced surgeons and delayed use of calcineurin inhibitors. New immunosuppressive protocols have further reduced the incidence of acute rejection to 30% in our series and to as low as 25% in the literature [8]. Moreover, with these regimens most rejection episodes were reversible with methylprednisolone. In our series, no kidney was lost due to rejection. Kidney biopsy was also an accurate, specific and very sensitive tool to monitor rejection of the pancreas. Futhermore, mastery of surgical techniques in pancreas transplantation has helped to lower

the high rate of pancreas complications and abdominal infections. This achievement influenced kidney outcome, since complications such as preservation pancreatitis, pancreatic leakage, pancreas thrombosis, abdominal abscesses and peritonitis were associated with interstitial kidney damage.

The latest analysis of the International Pancreas Transplant Registry compared patient and kidney graft survival rates for diabetic recipients of cadaver kidney transplants alone versus SPK recipients between 1994 and 1997. According to this analysis, the addition of a pancreas graft to the kidney transplant might increase the surgical risk of the transplant, but this risk is very small since patient and renal allograft survival rates were actually higher for SPK than for diabetic kidney recipients [10]. The results from the largest SPK series [8] show that patient and kidney graft survival in SPK recipients is higher than for kidney transplantation recipients of cadaver or even mismatched living donor grafts. Previous studies have demonstrated that in selected IDDM patients, SPK offers a longer life of a better quality as compared to kidney alone [7]. In reality, SPK has become the treatment of choice for IDDM patients with end-stage diabetic nephropathy [6].

Conclusions

The addition of a pancreas to the kidney transplant may increase the surgical risk. However, this risk is acceptable given the fact that both patient and kidney survival rates are higher for SPK patients than for kidney-alone recipients. Clearly, such encouraging results in SPK recipients indicate that a higher proportion of IDDM renal allograft recipients could also receive a pancreas. Physicians should therefore feel confident enough to influence eligible IDDM patients towards choosing SPK over kidney alone, even when the donated kidney is from a living source.

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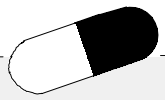
I hope for nothing, I fear nothing, I am free.

Epitaph on the gravestone of Nikos Kazantzakis, Greek novelist (1883–1957)

Capsule



Role for cholesterol in entry of *Mycobacteria* into macrophages

Mycobacteria are intracellular pathogens that can invade and survive within host macrophages, thereby creating a major health problem worldwide. The molecular mechanisms involved in mycobacterial entry are still poorly characterized. Gatefield and Pieters report that cholesterol is essential for uptake of *Mycobacteria* by macrophages. Cholesterol accumulated at the site of mycobacterial entry, and depleting plasma membrane cholesterol specifically inhibited mycobacterial uptake. Cholesterol also mediated the phagosomal association of TACO, a coat protein that prevents degradation of *Mycobacteria* in lysosomes. Thus, by entering host cells at cholesterol-rich domains of the plasma membrane, *Mycobacteria* may ensure their subsequent intracellular survival in TACO-coated phagosomes.

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