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Graft 2002; 5; 303

DOI: 10.1177/1522162802005005005

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The Effects of Pancreas Transplantation on the Course of Secondary Diabetic Complications

Paolo Fiorina and Antonio Secchi

Pancreas/kidney-pancreas transplantation (tx) is a procedure still affected by major risk. Positive effects of this procedure on diabetic complications were shown. Here the authors will discuss the positive effects of combined kidney-pancreas (KP) tx on glucose metabolism, long-term diabetic complications, and survival. A reduction of diastolic dysfunction was observed 4 years after tx in the KP (pre-tx: 73%, post-tx: 26%) but not in the kidney-alone (KA) group (pre-tx: 88%, post-tx: 77%). Normal endothelial function and lower intima media thickness were evident in the KP group. Fifty-one percent only of the KP group remain hypertensive at 1 year after tx, versus 81% of the KA group. Finally, among uremic type 1 diabetic patients enrolled for transplantation, those who received KP, KA, or remained on dialysis showed an actuarial survival at 7 years of 76.2%, 63.5%, and 39.6%, respectively. In conclusion, the KP group showed a better survival and reduced complications than the KA group.

ABBREVIATIONS

EDD	endothelial dysfunction
IDDM	insulin-dependent diabetes mellitus
IMT	intima-media thickening
NDD	nitrites dilation
SPK	simultaneous pancreas-kidney (transplantation)

Introduction

Pancreas/kidney-pancreas transplantation is a procedure still accompanied by major risk (i.e., surgery and immunosuppression) and associated with a higher incidence of cancer and infection¹⁻⁶ than the general population. Positive effects of these procedures on the quality of life,⁴ retinopathy,⁷ and nephropathy have already been shown.⁸

The International Pancreas Transplant Registry⁹⁻¹¹ shows that patient survival is better in simultaneous pancreas-kidney (transplantation) (SPK) patients than in patients undergoing kidney transplantation alone. One-year patient actuarial survival ranges from 90% to 95% (Fig. 1), and pancreas survival ranges from 80% to 90%^{9,10} (Fig. 1). It is interesting to note that, despite some initial fears, transplanted kidney survival is not impaired by the simultaneous transplantation of a pancreas: 1-year kidney actuarial survival of diabetic patients undergoing kidney-pancreas transplantation is similar to that achieved in diabetic patients undergoing kidney transplant alone.

Metabolic Effects of Pancreas Transplantation

When pancreas transplantation is successful, insulin is immediately withdrawn. Several investigations were performed in these patients to study this new condition. A transplanted pancreas is capable of secreting insulin and glucagon immediately after revascularization, which leads to the immediate and complete insulin-independence of patients receiving a whole pancreas, whereas patients receiving a segmental pancreas achieve insulin independence within a few weeks. Twenty-four-hour metabolic profiles show a near-normalization of blood glucose levels, with mild postprandial hyperglycemia in segmental pancreas.¹²⁻¹⁴ A normalization of intermediary metabolites (B-OH Butyrate, Lactate, Piruvate) is also observed. Fasting hyperinsulinemia is observed in these patients, as a consequence of the peripheral secretion of insulin and steroid administration. Glycated hemoglobin levels recover within a few months after transplantation and maintain normal values for several years. Studies performed with the method of the clamp technique show a re-

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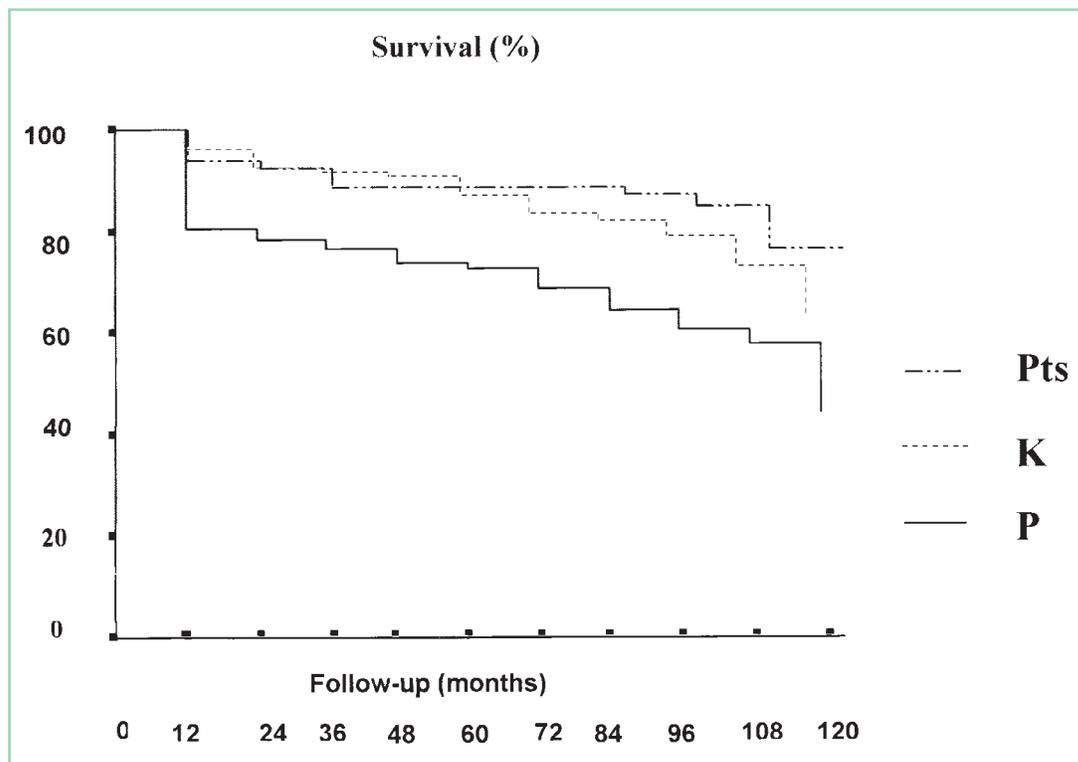


Figure 1. Patients (Pts), kidney (K), and pancreas (P) survival at San Raffaele Institute in type 1 diabetic uremic patients after combined kidney-pancreas transplantation. Patient survival was 92% at 1 year, 86% at 4 years, 66% at 10 years, respectively. Kidney survival was 92% at 1 year, 88% at 4 years, 75% at 10 years, respectively. Pancreas survival was 77% at 1 year, 71% at 4 years, 44% at 10 years, respectively (Ref. 28).

covery of peripheral insulin sensitivity and a normalization of hepatic glucose production.¹⁴ Some patients experience mild hypoglycemia as a consequence of a defect of counterregulation.¹⁵

Effects of Pancreas Transplantation on Long-Term Diabetic Complications

The main difficulty in studying the effects of pancreas transplantation on diabetic complications is related to the clinical conditions of these patients: they are frequently affected by end-stage degenerative complications. Since pancreas transplantation is frequently performed simultaneous to kidney transplantation in uremic diabetic patients, the recovery from uremia could overwhelm the transplanted pancreas effects.

Retinopathy

The majority of these studies were performed in patients already affected by proliferative retinopathy. Studies performed in diabetic patients under-

going pancreas transplantation alone have shown that the normoglycemia achieved with this approach does not prevent or reverse diabetic retinopathy.⁷ The same results were achieved when comparing diabetic patients submitted to kidney-pancreas transplantation with diabetic patients submitted to kidney transplantation alone.

Nephropathy

Diabetic nephropathy is the single most important cause of end-stage renal disease in Western countries. It results from the gradual accumulation of extracellular matrices in glomerular and tubular basement membranes and mesangial and interstitial tissues, as well as from hyalinosis of glomerular arterioles and global glomerular sclerosis. Two main types of studies on this topic can be identified. Studies examining patients submitted to pancreas transplant alone have shown that diabetic glomerular lesions, present on their own kidneys before transplantation, were not ameliorated by 5 years of

normoglycemia achieved through pancreas transplantation,¹⁶ whereas an improvement was observed in the same set of patients after 10 years of transplantation.⁸ Studies examining patients undergoing pancreas transplantation after successful kidney transplantation have shown that diabetic glomerular lesions are less severe than in patients submitted to kidney transplantation alone.¹⁷ Normoglycemia after pancreas transplantation ameliorated the glomerular and tubular lesions that characterize diabetic nephropathy in patients with their own kidney with reductions in the thickness of the glomerular and tubular basement membranes.¹⁷

Neuropathy

In patients affected by diabetic polyneuropathy, different studies have shown that the progression of neuropathy can be halted by successful pancreas transplantation.¹⁸⁻²⁰ It is more difficult to evaluate the effects of pancreas transplantation on peripheral neuropathy due to the fact that these patients are frequently affected by uremic polyneuropathy.²¹ Further studies performed on a longer follow-up period have shown that after an initial improvement in both groups of patients (kidney and SPK), only SPK patients show a further improvement of diabetic polyneuropathy.^{22,23} The severity of neuropathy before transplantation seems to play a relevant role: an improvement of neuropathy cannot be expected in patients affected by severe neuropathy before transplantation. The positive effect of pancreas transplantation on diabetic peripheral neuropathy was confirmed in a particular subset of patients. Five SPK patients were studied 2 years after the failure of the pancreas, which occurred at least 2 years after successful transplantation.²⁴ A progressive improvement of nerve conduction velocity was observed in these patients 2 years after successful transplantation. Two years after pancreas failure, when the kidney transplant was still functioning, nerve conduction velocity deteriorates to pretransplant levels, thus indicating the peculiar role played by the pancreas on peripheral neuropathy.²⁴

Cardiovascular Disease

Hypertension

When patients affected by arterial hypertension are submitted to kidney or SPK, only 51% of pa-

tients with a pancreas transplant remain hypertensive at 1 year, versus 81% of patients with kidney alone.²⁵ This difference is positively correlated with serum insulin levels and negatively correlated with HbA1c. Pancreas transplantation has a positive effect on hypertension.

Cardiomyopathy

Epidemiological studies have clearly demonstrated that diabetic patients are at increased risk for cardiovascular morbidity and mortality. Diastolic filling, more than systolic function, is frequently impaired in these patients. The effects of glycometabolic control achieved by pancreas transplantation on left ventricular function were evaluated in uremic insulin-dependent diabetes mellitus (IDDM) patients.²⁶ Left ventricular systolic and diastolic functions were evaluated with radionuclide ventriculography in a subset of 42 SPK and 26 kidney-alone recipients. As controls, 20 IDDM were chosen. Left ventricular ejection fraction was normal in all the patients, with statistically significant higher values in SPK patients with 4 years of graft function ($75.7\% \pm 1.8\%$) than in kidney-alone with 4 years of graft function ($65.3\% \pm 2.8\%$, $P < 0.05$) and IDDM patients ($61.3\% \pm 3.7\%$, $P = 0.004$). In patients with 2 and 4 years of graft function, normal diastolic parameters were evident in SPK but not in kidney-alone and in IDDM (SPK vs. kidney-alone and vs. IDDM: peak filling rate = 4.46 ± 0.15 EDV/sec vs. 2.73 ± 0.24 EDV/sec, $P < 0.05$ and vs. IDDM = 3.39 ± 0.30 EDV/sec, $P = 0.007$; time to peak filling rate = 141.9 ± 7.8 msec vs. 209.4 ± 13.5 msec, $P < 0.05$ vs. 162.0 ± 7.5 msec). Diastolic dysfunction was observed in SPK and kidney-alone patients with 6 months of follow-up, whereas a statistical significant reduction of the rate of diastolic dysfunction was observed 4 years after transplant in SPK (pretransplant: 73%, posttransplant: 26%), but not in kidney-alone transplantation (pretransplant: 88%, posttransplant: 77%) (Fig. 2).²⁶ From these data, it appears that SPK transplantation exerts positive effects on left ventricular function and blood pressure.

Atherosclerotic Risk Factors and Endothelial Dysfunction

The effects of pancreas transplantation on atherosclerotic risk factors, endothelial dysfunction

RETINOPATHY

Noninflammatory degenerative disease of the retina

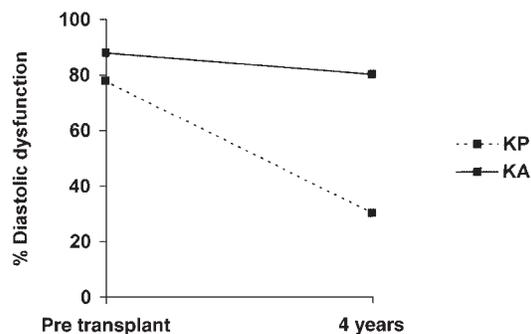


Figure 2. Improvement of diastolic dysfunction is observed after kidney-pancreas (KP) but not after kidney-alone (KA) transplantation in uremic type 1 diabetic patients ($P < 0.05$) (Ref. 26).

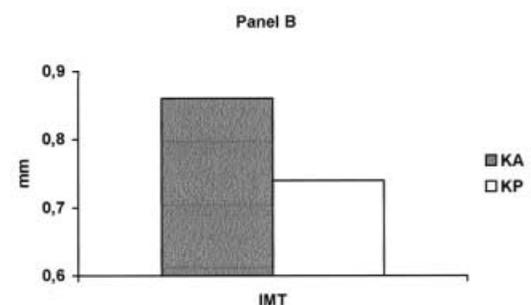
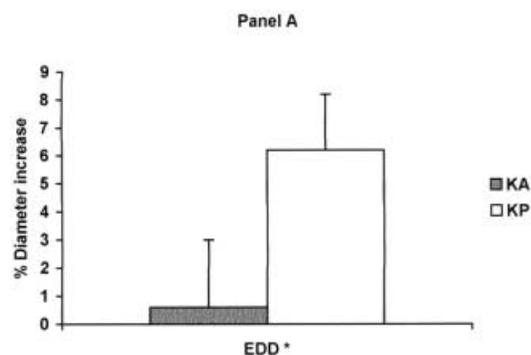


Figure 3. Endothelial dependent dilation (EDD, Panel A) and intima media thickness (IMT, Panel B) after kidney-pancreas (KP) or kidney-alone (KA) transplantation in type 1 diabetic uremic patients. After KP, but not KA, transplantation recovery of EDD and a reduction of IMT were evident (Ref. 27).

(EDD), and progression of intima-media thickening (IMT) were also evaluated in IDDM patients. Sixty patients submitted to SPK transplantation and 30 to kidney-alone transplantation were studied.²⁷ Atherosclerotic risk factors, Doppler-echographic evaluation of IMT, and assessment of endothelial function with flow-mediated dilation (EDD) and nitrates dilation of the brachial artery were evaluated. Kidney-alone, but not SPK, showed higher values of HbA1c, tHcy, vWF levels, ddf, fibrinogen, and triglycerides. As regards endothelial function, SPK, but not kidney-alone, showed a normal EDD (Fig. 3, Panel A). Moreover, IMT was reduced in kidney-pancreas (KP) group rather than in kidney-alone (Fig. 3, Panel B). From these data, it appears that IDDM patients undergoing SPK transplantation have a lower atherosclerotic risk profile than IDDM patients undergoing kidney-alone transplantation. These differences are strongly correlated with metabolic control, lower tHcy levels, reduced ddf, and vWF levels. Normal endothelial-dependent dilation and reduced intima media thickness were observed in KP transplanted type 1 diabetic patients and not in kidney-alone transplanted type 1 diabetic patients. SPK transplantation seems to play a protective role toward atherosclerotic risk factors and progression of macroangiopathy when compared to kidney-alone transplanted patients.²⁷ Endothelial cells are the origin of all circulating vWF and increased vWF plasma levels may reflect the extent of vascular damage. Higher values of IMT present in the kidney-alone

group could be an important index of future coronary and cerebral ischemic diseases. It is known that intimal thickening precedes the atherosclerotic lesions: for each 0.1 mm of IMT, the risk of acute myocardial infarction increased by 11%. Increased IMT could be the final step of the cascade induced by the enhanced pro-thrombotic state.²⁷

Survival and Cardiovascular Death Rate

In a recent study, among 345 uremic IDDM patients on a waiting list for kidney-pancreas transplantation, 115 underwent kidney-pancreas transplantation, 34 underwent kidney transplantation alone, whereas 196 patients remained on dialysis. Actuarial survival and causes of death were recorded

DIABETIC NEUROPATHY

Combined sensory and motor neuropathy, typically symmetric and segmental, and involving autonomic fibers

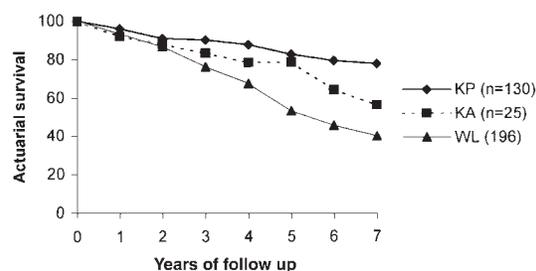


Figure 4. Patient actuarial survival rate in 130 kidney-pancreas (KP), in 25 kidney alone (KA), and in 196 dialysed type 1 diabetic (WL). (Kidney-pancreas versus dialysed, $P = 0.01$, $df = 5.8$.) Patients after KP, but not KA, transplantation showed a better survival than WL patients (Ref. 28).

over a period of 7 years. Seven-year survival rate was 76.2% for SPK, 63.5% for kidney-alone, and 39.6% for dialysed group ($P = 0.01$) (Fig. 4). Cardiovascular death rate was 7.8% in SPK, 14.7% in kidney-alone, and 16.1% in dialysed (SPK versus dialysed, $P = 0.05$).²⁸

Finally, the rate of lethal neoplasm observed in this study is similar to that reported for uremic patients, showing that SPK and kidney-alone transplantations do not enhance neoplasm death rate when compared to dialysed patients.²⁹ In conclusion, SPK-transplanted patients showed better survival than patients transplanted with the kidney alone and waiting-list patients. This was associated with a low prevalence of cardiovascular events in patients undergoing SPK transplantation.

Conclusion

Pancreas transplantation is associated with an amelioration of cardiovascular death rate. Moreover, SPK transplantation could exert a positive effect on diabetic nephropathy, neuropathy, soluble atherothrombotic risk factors, atherosclerosis, endothelial dysfunction, and diastolic dysfunction.

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