Original Article

Simultaneous kidney-pancreas transplantation: the Parma Center experience

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Abstract. *Background and aim:* Diabetes mellitus is one of the major causes of end stage renal disease. After 10-15 years from the onset 30% of diabetic patients present nephropathy, and once haemodialysis is required, morbidity is particularly high and long-term survival is lower than in non-diabetic patients. Currently, it is demonstrated that simultaneous pancreas-kidney transplantation (SPK) shows beneficial effects on patient survival, on some diabetic degenerative complications and on the quality of life. Aim of the work is to report our experience in pancreas transplantation. *Methods:* From June 1998 to June 2005 17 type I diabetic uremic patients underwent SPK. Donor selection considered hemodynamically stable young patients without cardiac arrest or vasopressor drug excess and with a brief Intensive Care Unit hospitalization. Average donor age was 26 years (range 16-38). The cause of death was trauma for 14 donors (82,4%) and spontaneous cerebral hemorrhage for 3 donors (17,6%). Average pancreas cold ischemic time was 716 minutes (range 320-968). *Results:* No patient mortality was observed. No primary or delayed graft function was observed both for pancreas and kidney. Biopsy proved the occurrence of acute rejection episode in one patient (5,8%). Five surgical (29,4%) and 2 medical (11,7%) complications developed. At a median follow-up of 36,4 months (range 4,2-88) patient survival rate was 100%. Pancreas and kidney graft survival rate was 76,5% and 94,1%, respectively. All patients referred an improvement in their quality of life. *Conclusions:* SPK represents a well-established therapy for uremic type I diabetes mellitus since it improves patient survival in selected recipients. Our experience, as reported in literature, confirm that a successful pancreas transplantation not only brings the recipient back to normal glycemic levels, but it also improves the patient's quality of life by stabilizing some of the secondary complications of diabetes. (www.actabiomedica.it)

Key words: Transplantation, pancreas, surgery, diabetes mellitus

Introduction

Pancreas transplantation was first described by Kelly and Lillehei in 1967 at the University of Minnesota (1), but initial patient and graft survival rates were poor. Different factors have led to improvements in patient and graft survival, including donor and recipient selection, advances in surgical techniques, preservation methods, immunosuppresion, rejection diagnosis, and treatment (2). As a consequence, the number of pancreas transplantations has progressively increased, especially in the United States (more than 1000 pancreas transplantations per year). Unfortunately, in Italy the number of pancreas transplantations performed each year is much lower (< 100 per year).

There are three main types of pancreas transplantation: 1) simultaneous pancreas-kidney transplantation (SPK), in which both organs are transplated in type I diabetes mellitus patients with end-stage or pre-emptive renal disease; 2) pancreas after kidney transplant (PAK), in which a pancreas from a cadaveric donor is transplanted in an insulin-dependent dia-

betic patient with a well functioning kidney transplant; 3) pancreas transplant alone (PTA) in a type I diabetic patient with frequent and severe episodes of hypoglicemia, hyperglicemia or ketoacidosis and two or more degenerative complications including evidence of early diabetic nephropathy but with preserved renal function (creatinine clearance > 70 ml/min).

Diabetes mellitus is one of the major causes of end stage renal disease. After 10-15 years from the onset of disease 30% of diabetic patients present nephropathy, and once haemodialysis is required, morbidity is particularly high and long-term survival is lower than in non-diabetic patients (after 5 years of haemodialytic treatment only 30% of diabetic patients is still alive).

Presently, it is clearly demonstrated that SPK shows beneficial effects on patient survival rate, on some diabetic degenerative complications (retinopathy, neuropathy and nephropathy), and on the quality of life. Therefore, SPK has become the treatment of choice in selected patients. The aim of this study was to review our experience in SPK.

Table 1. Contra-indications for recipient selection

- Severe coronaropathy not suitable for treatment, ejection fraction < 40%, myocardial infarction < 6 months
- Age > 55 years
- BMI > 30 Kg/m2
- Ethanol or drug abuse
- HIV 1,2 positivity
- Active infection
- Neoplastic disease
- Severe liver or lung disease
- Major psychiatric disorders

Table 2. Contra-indications for donor selection

- Age > 45 years
- Neoplastic disease
- Active infection
- HIV 1,2 positivity
- Diabetes mellitus
- Pancreatic trauma or surgery
- Pancreatitis or pancreas disease
- Fatty infiltration
- BMI > 30 Kg/m2
- Prolonged hypotension and/or cardiac arrest

Material and methods

From June 1998 to June 2005 17 type I diabetic uremic patients (10 males and 7 females) underwent SPK. Mean age was 43 years (range 33-54). At the time of transplantation, mean duration of diabetes mellitus was 25 years (range 11-36), wherease mean duration of haemodialysis treatment was 3,4 years (range 0,5-22 months). Three patients (17,6%) were transplanted prior to dialytic treatment (pre-emptive treatment).

Thirteen patients (76,5%) presented hypertension, four (23,5%) asymptomatic ischemic cardiopathy, three (17,6%) peripheral vascular disease, fifteen (88,2%) retinopathy, five (29,4%) peripheral neuropathy, and two (11,8%) autonomic neuropathy. The main contra-indications for recipient selection are shown in table 1.

Donor selection considered hemodynamically stable young patients (age < 40 years) without cardiac arrest or vasopressor drug excess and with a brief Intensive Care Unit hospitalization. Final graft evaluation was performed at procurement. Contra-indications for donor selection are shown in table 2.

Average donor age (11 males and 6 females) was 26 years (range 16-38). The cause of death was trauma for 14 donors (82,4%) and spontaneous cerebral hemorrhage for 3 donors (17,6%).

Average pancreas cold ischemic time was 716 minutes (range 320-968), whereas average warm ischemic time was 51 minutes (range 30-75). Perfusion solution was University of Wisconsin in 3 and Celsior in 14 procedures.

During bench surgery a donor Y iliac bifurcation was used for the reconstruction of the pancreas graft. Donor hypogastric and external iliac artery were anastomised to the splenic and superior mesenteric artery of the pancreas, respectively.

The pancreas was placed intraperitoneally in the right iliac fossa and the renal graft was placed in the left iliac fossa. The portal vein was anastomised to the external iliac vein in 13 patients and to the caval vein in 4 patients. Arterial revascularization of the pancreas allograft was performed to the common or external iliac artery (end-to-side). Exocrine drainage was

achieved through a side-to-side duodenal-ileal anastomosis with a Roux-en-Y loop in 4 patients and without a Roux-en-Y loop in 13 patients. Kidney transplantation was carried out according to the standard technique.

Immunosuppression was induced by antithymocyte globulins (Thymoglobulin®) in all patients, whereas maintenance therapy was achieved by cyclosporine-based immunosuppression associated with mycophenolate mofetil (or azathioprine) and steroids in 12 patients or tacrolimus with mycophenolate mofetil plus steroids in 5 patients.

Follow-up was based on clinical evaluation, laboratory testing and neurological, ophthalmologic and cardiovascular examination.

Results

No patient mortality was observed. No primary or delayed graft function was evidenced both for pancreas and kidney. Biopsy proved the occurrence of acute rejection episode in one patient (5,8%) that was successfully treated by 5-days of anti-thymocyte globulins administration. Five surgical (29,4%) and 2 medical complications (11,7%) developed. Surgical complications included 1 venous thrombosis (5,8%), 1 arterial thrombosis (5,8%), 1 iliac graft pseudoaneurysm (5,8%), 1 duodenal stump leakage (5,8%) and 1 urinary leak (5,8%). Graft pancreatectomy was necessary in 4 patients (23,5%). Overall 6 re-laparotomies were performed (35,3%) in 5 patients. Medical complications consisted in 1 acute pancreatitis and 1 inferior limb deep venous thrombosis.

At a median follow-up of 36,4 months (range 4,2-88) patient survival rate was 100%. Pancreas and kidney graft survival rate was 76,5% and 94,1%, respectively. One patient underwent a second kidney transplant because of graft loss.

In functioning SPK (13) patient's glycemia, glycosilated haemoglobin, C-peptide, and renal function were always normal. Average arterial pressure value was 130/80 mmHg (range 140-120/70-85) and 11 patients (84,6%) reduced or suspended antihypertensive drugs.

All patients referred an improvement in their quality of life. Diabetic neuropathy improved in 2 patients (15,4%) and stabilized in 8 patients (61,5%). Retinopathy remained stable in 7 patients (53,8%) whereas it progressed in 3 patients (23%). No diabetic nephropathy recurrence occurred. Peripheral arteriopathy advanced in 3 patients (23%). No cerebral or cardiovascular event was observed.

Discussion

Until December 2004 over 23.000 pancreas transplantations had been performed worldwide, the majority of them in combination with a kidney transplant (SPK). Patient and pancreas survival rates at 1 and 5 years were 95%, 85% and 90%, 70% respectively, similar to those achieved with the transplantation of other solid ogans (3). Although our experience is preliminary, a 100% patient survival rate at three years of median follow-up is remarkable.

These encouraging results have been strengthened by an increasing number of reports on the capability of SPK to prolong type I diabetic uremic patient survival (4, 5). At a 10-year follow-up Oyo et al pointed out that expected lifetime for SPK patients is 23 years versus only 8 years in waiting-list patients (6). Moreover, it is reported that a well-functioning SPK improves patient survival by 7 to 10 years compared with patients with cadaver donor kidney transplant, SPK with loss of pancreas graft function, and dialysis in type I diabetes patients waiting for a transplant (7). SPK should be considered as a life-saving procedure for type I diabetes and end-stage renal failure patients.

Living-donor kidney transplant offers similar patient survival as SPK, but without the protective effect achieved by pancreas graft. In fact, recurrent diabetic nephropathy is found 2 years after kidney transplantation in diabetic patients, while diabetic nephropathy has never been observed in kidney graft of a well-functioning pancreas allograft (8).

Surgical complications are still high (about 35%), as well as re-laparotomy with a 10% related mortality. (9) Major complications are acute pancreatitis (35%), abdominal infection (20%), vascular thrombosis (12%), and anastomotic leakage (10%). Our surgical complications, and re-laparotomy rate was 29,4% and

35,3% respectively. Technical failure is still one of the leading causes of pancreas graft loss. In our experience four grafts failed (23,5%) because of thrombosis, leakage and haemorrhagic complications. Several risk factors contribute to surgical complications after pancreas transplants such as the underlying disease itself, recipient and donor age, the transplant procedure, and the extended anti-T-cell induction therapy (9).

Regarding immunosuppression, great progress has been made in the diagnosis and treatment of acute rejection in recent years, especially after the introduction of tacrolimus and mycophenolate mofetil (10). In the last years, pancreas graft loss rate due to rejection was 2% (3) We observed only one acute rejection episode (5,8%), that was successfully treated with anti-thymocyte globlins.

Another important issue in SPK is the improvement in the quality of life. In particular, diabetes-related quality of life is clearly improved by the association of a pancreas to a kidney transplant (11). The suspension of exogenous insulin administration and dietetic limitations along with the removal of acute metabolic complications permits a remarkable improvement in the quality of life. All our patients referred an improvement in their quality of life, the majority of them also resuming social and working life. However, overall quality of life depends on the specific expectation of the patient and whether or not it is achieved, especially considering postsurgical morbidity which is often high in SPK recipients (11, 12).

Pancreas transplantation has beneficial effects on glucose regulation since it restores pancreatic islet function. In most recipients glucose concentration and HbA1C values normalize after successful SPK. Most importantly, in response to hypoglicemia glucagon and epinephrine secretion and hepatic glucose production return to normal. These effects result in a normalized response to hypoglicemia and symptom recognition (13, 14).

Several studies have investigated the effects of SPK on diabetic degenerative complications. Regarding diabetic retinopathy, the majority of patients had been transplanted when retinic lesions were probably irreversibly settled. After 3 or more years of pancreas graft function, however, less retinal surgery is required, fewer new vitreous hemorrhage are observed, and visual acuity is improved compared with kidney transplant alone (11). Similar results have been pointed out in our patients, with 53% of patients showing a stabilized retinopathy.

Because of the ability to assure normoglycemia, SPK has a protective effect on diabetic nephropathy avoiding the occurrence of the typical diabetic glomerular lesions (15). Thus, in SPK the renal graft is protected from hyperglycemia damage and diabetic nephropathy recurrence. Moreover, it is reported that typical diabetic nephropathy is reversible in native kidneys after 5-10 years of successful PTA (16).

SPK may arrest or improve diabetic neuropathy. Navarro documented an improvement in cardiorespiratory reflexes and nerve conduction after SPK with a lower rate of sudden death (17). Heart rate variation, gastric emptying and skin temperature regulation have all been reported to improve (18). Two patients in our experience showed an improvement of neuropathy that was documented by electromyography, while diabetic neuropathy remained stable in the other ten patients.

SPK shows positive effects on the cardiovascular system, especially on hypertension and cardiac function. In fact, several studies have demonstrated the restoration of normal blood pression or lower grade hypertension after pancreas transplantation. It seems that glycometabolic control may have positive effects on the pathogenesis of diabetic hypertension (19). Other studies have showed beneficial effects on the cardiovascular system: carotid intima media thickness improved in 2 years after SPK (20), left ventricular ejection fraction (21) and diastolic dysfunction (22) returned to normal or improved after SPK compared with type I diabetes recipients receiving only a kidney transplant.

In contrast, macrovascular disease (coronary heart disease, peripheral vascular disease) can progress after pancreas transplantation in spite of improvements in lipid profiles, blood pressure, and glycemic control (11, 23).

In conclusion, SPK represents a well-established therapy for uremic type I diabetes mellitus patients since it improves patient survival in selected recipients. Successful pancreas transplantation not only brings the recipient back to normal glycemic levels,

but it also improves the patient's quality of life by stabilizing some of the secondary complications of diabetes. Our initial experience confirms these results according to that reported in literature.

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