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Pancreas-Kidney Transplantation: Analysis of 150 patients from one Centre in Portugal

Transplantação Reno-Pancreática: Análise de 150 doentes de um Centro em Portugal

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ABSTRACT

Introduction: Simultaneous pancreas-kidney transplantation (SPKT) outcomes are conditioned in the short-term mostly by post-operative complications. In the long-term, cardiovascular (CV) disease and immunological loss are the main limitations to transplant survival. **Aims:** To analyse retrospectively the results from 150 SPKT performed at our centre. **Patients and Methods:** The 81 females and 69 males had a mean age of 35±6 years; they were diabetic for 24±6 years and had been on dialysis for 30±21months (except 5 preemptive). Anti-lymphocyte globulin, tacrolimus, mycophenolate and steroids were used as immunosuppressive therapy. Deceased-donor mean age was 28±11 years. In 28.7% the transplant was performed with 6 HLA-mismatches. **Results**: Acute rejection's incidence was 16%. Ten SPKT patients died; infection was the leading cause of death (five cases), followed by Cardiovascular/cerebrovascular disease (three cases). In 21 patients the pancreas failed, mainly due to thrombosis or bleeding (11 cases), and infection (five cases); in two it was due to late acute rejection. In four patients only the kidney failed, due to chronic rejection. Five patients lost both grafts, from late acute rejection in four and thrombosis in one. We analyzed the 110 SPKT patients (73.3%) with both grafts functioning. Their mean serum creatinine was 1.2±0.4mg/dl; creatinine-clearance was 76±24 ml/min; fasting glycaemia was 81±10mg/dl; and HbA1c was 5.3±0.4%. Hypertension has been treated in 47.2% of patients, in the majority (28.2%) with only one drug. Hyperlipidaemia was observed in 19.1% and excessive weight (›25kg/m2) in 17.3%. **Conclusions**: From our cohort of SPKT, 93.3% of patients are alive, 73.3% have both grafts functioning. Rejection was the main cause of late pancreas loss. Early mortality was due to infection (3.3%). CV/cerebrovascular disease was the main cause of late mortality (2%). The prevalence of hyperlipidaemia and overweight was inferior to 20%. Hypertension was the most frequently found CV risk factor.

Key-words: graft loss; long-term results; pancreas-kidney transplantation; patient death

RESUMO

Introdução: A sobrevivência do transplante de rim-pâncreas (TRP) é condicionada na fase precoce pelas complicações inerentes ao próprio acto cirúrgico. A sua perda tardia deve-se essencialmente a morte por doença cardiovascular (CV), ou imunológica. **Objectivos**: Analisámos retrospectivamente os resultados dos 150 TRP realizados no nosso centro. **Doentes e métodos**: Os 81 doentes do sexo F e 69 do sexo M, tinham uma idade média de 35±6 anos; eram diabéticos há 24±6 anos; e estavam em diálise há 30±21meses (excepto 5 *preemptive*). A terapêutica imunossupressora consistiu em globulina anti-linfocítica, tacrolimus, micofenolato e corticóides. A média de idades do dador (cadáver) foi 28±11 anos. Em 28.7% o transplante foi realizado com 6 incompatibilidades HLA. **Resultados**: A incidência de rejeição aguda foi de 16%. Faleceram 10 doentes: a causa mais frequente foi a infecciosa (5 casos), seguida da CV/cerebrovascular (3 casos). Em 21 casos houve falência isolada do pâncreas maioritariamente por trombose ou hemorragia (11 casos) e por infecção (5 casos), em 2 casos por rejeição aguda tardia. Em 4 TRP ocorreu falência isolada do rim, por rejeição crónica. Em 5 casos ambos os enxertos faliram: por rejeição aguda tardia 4 doentes; trombose 1 doente. Os 110 TRP (73.3%) que mantêm ambos os enxertos funcionantes, têm creatinina de 1.2±0.4mg/dl; clearance da creatinina de 76±24 ml/min; glicemia em jejum de 81±10mg/dl; e HbA1c de 5.3±0.4%. Apresentam hipertensão 47,2%, a maioria (28,2%) requerendo apenas 1 fármaco. Hiperlipidemia verificou-se em 19,1% e excesso de peso (›25kg/m2) em 17,3% dos doentes. **Conclusões**: Deste grupo de TRP estudado, estão vivos 93.3% e 73.3% têm ambos os enxertos funcionantes. Rejeição foi a principal causa de perda tardia do pâncreas. A mortalidade precoce deveu-se a infecção (3.3%). Doença CV/cerebrovascular foi a causa mais frequente de mortalidade tardia (2%). A prevalência de hiperlipidemia e excesso de peso foi inferior a 20%. Hipertensão foi o factor de risco CV mais frequentemente encontrado.

Palavras-chave: morte do doente; perda de enxerto; resultados a longo-prazo; transplantação reno-pancreática

INTRODUCTION

Simultaneous pancreas-kidney transplantation (SPKT) is the best treatment for type 1 diabetic patients with end-stage renal disease who have the conditions for this kind of transplant. The results of SPKT are better than those obtained from other modalities of pancreas transplantation, such as pancreas after kidney (PAK), or pancreas transplantation alone (PTA)[1]. A successful SPKT frees the patient from insulin and dialysis-dependence and avoids the life-threatening hypoglycaemic episodes. This may represent a significant improvement on their impaired quality of life. It is unquestionable that SPKT leads to a significant improvement in patient survival, when compared to those staying under dialysis and insulin, or even compared to those who underwent a cadaveric kidney alone transplant[2]. Moreover, the pancreas transplant may stop the progression or even ameliorate the various secondary diabetic complications[1,2].

Outcomes of SKPT have improved over time, in parallel with other organ transplants[1,2,3]. However, patient and graft loss after SPKT, namely in the early phase after surgery, is higher than in kidney transplantation alone. Thrombotic and infectious complications are the leading causes of graft failure or even patient death in the short-term[1]. Cardiovascular or cerebrovascular disease[2,3] and also infection[1,2] are the main limitations for long-term SPKT patient survival. Immunological loss[3] and death with a functioning graft[3] represent the main causes of graft failure in the long-term. It is well known for these patients the increase in mortality after graft loss: the relative risk of death increased more than 17-fold in recipients whose kidney failed and more than 3-fold in recipients whose pancreas failed[1].

The aim of this study was to analyze the outcome of the SPKT performed at our centre and to search for possible factors associated with the outcome.

PATIENTS AND METHODS

From May 2000 to October 2012, 150 type 1 diabetic patients underwent SKPT at the Transplantation Department of our Hospital. All the procedures were performed using grafts form deceased donors, both grafts from the same donor, and using systemic-enteric drainage (venous drainage to the iliac vein; exocrine drainage through an enteric anastomosis of the pancreatic-duodenal arch). Only patients with a minimum follow-up of 3 months were considered for this retrospective analysis.

Results are presented as mean ± standard deviation for continuous, normally distributed variables, and as percentages for categorical data. Patient survival was determined from the time of SPKT until death or end of follow-up. Death-censored kidney graft survival was determined from the time of kidney transplantation until kidney retransplantation, return to dialysis, or end of follow-up. Death-censored pancreas graft survival was determined from the time of SPKT until pancreas failure or end of follow-up. Survival analysis was performed using the Kaplan-Meier (product-limit) estimator of survival.

These 150 patients, 81 females and 69 males, had a mean age of 35±6 years at transplantation date. They were diabetic for 24±6 years; and had been on dialysis for 30±21months, excepting five patients who received a pre-emptive transplant. Anti-lymphocyte globulin, tacrolimus, mycophenolate and steroids were used as induction therapy. Deceased-donor mean age was 28±11 years. In 28.7% of the patients the transplant was performed with 6 HLA-mismatches.

RESULTS

The median admission time was 20 days. Global acute rejection incidence (for kidney, pancreas or both grafts) was 16%. Delayed kidney graft function, defined for dialysis need in the first week, occurred in 16%. In the vast majority of patients whose pancreas did not have complications, insulin administration could be stopped during the first hours after transplantation (median 0 days).

In 21 patients the pancreas failed, mainly (16 cases) in the very early period (‹3 months) due to thrombosis (eight cases) or bleeding (three cases) and local infection leading to graft removal (five cases); late pancreas loss was due to late acute rejection (two cases), atheroembolism after coronary angiography using lower limb access (one case) and due to unknown cause in two cases.

In four patients only the kidney failed, due to chronic rejection, and these were late losses. In five others, both grafts failed: in one case it was an early loss due to thrombosis of both grafts; and in four it was due to late (› 6 months) acute rejection – in three cases we have confirmed patient non-compliance to medication. Tacrolimus trough levels were undetectable or markedly below the expected for this follow-up time (7-9 ng/ml).

Death occurred in 10 patients: in five during the early period, and later in five others. Analyzing the causes of patient death from the point of view of the different periods (‹ 12months vs. › 12 months): early deaths were due to post-operative sepsis (three cases), aspergillosis (one case), and unclear cause (one case); late deaths were caused by myocardial infarction (two cases), stroke (one case), CMV disease (one case) and digestive haemorrhage (one case). Globally, infection was the leading cause of death (five cases), followed by cardiovascular (CV) or cerebrovascular disease (three cases). Table 1 summarizes the causes of graft failure and patient death.

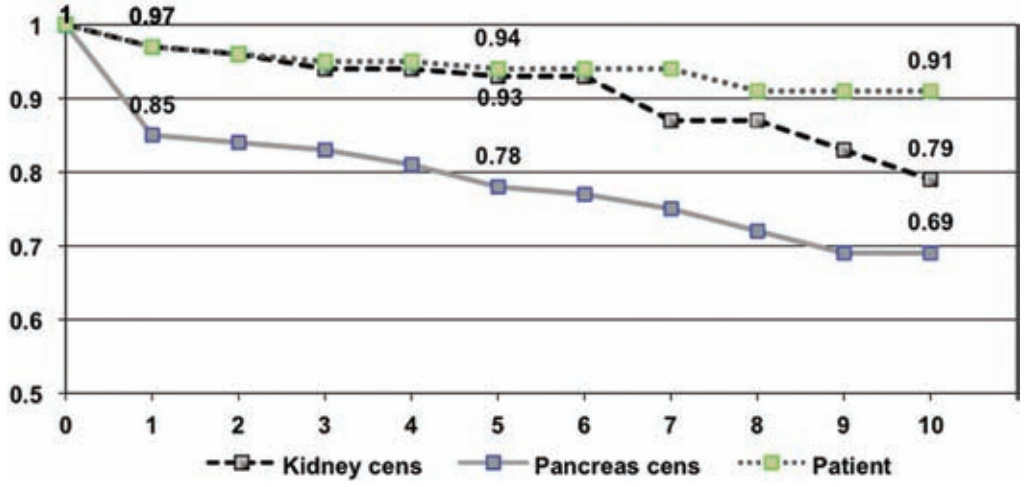
At the last visit, 110 SPKT patients (73.3%) maintained both grafts functioning. Their mean serum creatinine is 1.2±0.4mg/dl; creatinine clearance is 76±24 ml/min; fasting glycaemia is 81±10mg/dl; and HbA1c=5.3±0.4%. Hypertension has been treated in 52 SPKT (47.2%), in the majority (31SPKT – 28.2%) with a single drug, mostly a beta-blocking agent. Hyperlipidaemia was observed in 23 patients (20.9%) and excessive weight (› 25kg/m2) in 19 patients (17.3%).

Survival rates (death-censored) obtained for this cohort of SPKT at our centre for patient, kidney and pancreas, respectively, were: at 1 year 97%, 97% and 85%; at 5 years 94%, 93% and 78%; and at 10 years 91%, 79% and 69% (Graph 1).

Table 1

Causes of graft failure and patient death.

(Total =150 SPK)	Timing of occurrence	Main cause	Specific cause
Pancreas loss (n=21)	Very early* loss (n=16) *(follow-up <3 months)	Thrombosis (n=8)	Pancreas graft thrombosis (n=8)
		Bleeding (n=3)	Peri-graft bleeding (n=3)
		Infection (n=5)	Pancreatic leak/ abdominal infection (n=5)
	Late loss (n=5)	Acute rejection (n=2)	Unsolved acute rejection (n=2)
		Atheroembolism (n=1)	(after coronariography)
		Unknown (n=2)	
Kidney loss (n=4)	Late* loss (n=4) *(>6 months)	Chronic rejection (n=4)	
Pancreas and kidney loss (n=5)	Early loss (n=1)	Thrombosis (n=1)	Pancreas and kidney graft thrombosis (n=1)
	Late* loss (n=4) *(>6 months)	Acute rejection (n=4)	Non-compliance confirmed (n=3)
			Non-compliance unconfirmed (n=1)
Patient death (n=10)	Early death (n=5)	Infection (n=4)	Post-operative sepsis (n=3)
			Aspergillosis (n=1)
		Unknown (n=1)	
	Late* death (n=5) *(follow-up >12 months)	Infection (n=1)	CMV disease (n=1)
		Cardiovascular / cerebrovascular disease (n=3)	Stroke (n=1)
			Myocardial infarction (n=2)
		Digestive haemorrhage (n=1)	



Graph 1

Patient and graft survival rates of the 150 SPKT (death-censored)

DISCUSSION

There are no longer any doubts that SPKT offers the best results to treat type 1 diabetic patients with end-stage renal disease. The last position statement of the American Diabetes Association[4] has confirmed, again, their previous recommendation[5] of pancreas transplantation for these patients, preferably done simultaneously to a kidney transplant, given the better pancreas survival of SPKT[4,5]. Also from a point of view of quality of life, SPKT can provide significant benefit[6,7]. The successive International Pancreas Transplant Registry (IPTR) reports have confirmed the progressive improvement in SPKT outcome over

the past decades[1,8,9]. However, it seems that a maximum and a plateau was reached in the survival curves, because no further significant improvements have been observed in the last 10 years[1].

Pancreas graft outcome is determined mostly by the success in early post-operative period. Thrombosis, bleeding, pancreatic leaks and infection after surgery are normally defined as technical failures. In the last IPTR[1], near 9% of the losses were reported as due to technical failure. It is 10.7% in our own experience (16/150 patients), not too different from the international results recorded on 25000 SPKT[1]. Thrombosis remained the main cause of early pancreas graft loss, as reported by large centers[2,3].

Pancreas losses due to acute rejection were observed in our study group in 6 SPKT (4%), but in half of them non-compliance of the patients to immunosuppression was verified. Blindness or very impaired vision may be a real problem for these patients to strictly follow the medication and this was the case in at least one patient. Thus, if we exclude the "expected" losses associated with confirmed/confessed non-compliance, we obtain a rate of 2% of "unexpected" acute rejection loss, similar to that observed in large series[1,8].

Kidney graft loss occurred in the late period in all but one of the 9 patients of our study group with kidney failure. Rejection was the main cause of these late losses and this has also been observed by others[2,3].

Systemic vascular disease, CV and cerebrovascular disease are strongly associated with an increased risk of patient death[2]. In our own experience, infection in the early period (3.3%) and CV/cerebrovascular disease (2%) in the late period were the leading causes of patient death. These same reasons for patient death were reported by the IPTR[1]; and the authors observed that death due to infection peaked between 3 and 12 months.

Hypertension was the most frequently found CV risk factor, although its prevalence was inferior to 50% and in only 28.2% requiring more than one drug. Beta-blocking agents were the most often prescribed drugs with anti-hypertensive properties, even when the goal is not necessarily to treat hypertension. In fact, in some of these patients high blood pressure was not recorded. However, it is our policy to maintain this medication, given its cardio-protective effects, especially if the patients had previously been under this drug. The prevalence of hyperlipidaemia and excessive weight was inferior to 20% in our SPKT patients.

Compared to kidney transplantation alone, SPKT is known to have more complications: a higher rate of readmissions[10] and early surgical complications that may lead to relaparotomy in more than 30% of cases[3,11]. Despite these feared complications and the initial increased risk (compared with those patients in the waiting list for transplant), transplanted patients perform better at 1 year[12]. Moreover, and against initial concerns, 10-year results do not confirm a higher mortality of diabetics after SPKT versus kidney transplantation alone[13]. The improvement in quality of life and the effect on long-term diabetic complications justify the option for surgery[12]. The developed LYFT scores (life years from transplant), which assess life enhancement achieved by each transplant, was greater for diabetics with a SPKT than with kidney transplantation alone[14]. Thus, it is currently stated that SPKT is the most cost-effective treatment for patients with type 1 diabetes and end-stage renal disease[15].

The authors of the latest IPTR reported a 10-year patient survival over 70%[16]. Considering only SPKT recipients who reached the 1-year mark with both grafts alive, they reported a 10-year survival rate around 66 % for the kidney and 62% for the pancreas grafts. In a more recent analysis, the 10-year pancreas graft function for SPKT was 68%[16]. We have published the 10-year results of SPKT at our centre two years ago[17] and they were not inferior to the international results. Those good outcomes and survival rates are validated by remain confirmed in this cohort of patients with extended follow-up.

Conflict of interest statement: none declared

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