Transpl Int (2003) 16: 128–132
DOI 10.1007/s00147-002-0501-2

ORIGINAL ARTICLE

Guido Woeste
Christoph Wullstein
Olaf Pridöhl
Peter Lübke
Rene Schwarz
Kay Kohlhaw
Wolf O. Bechstein

Incidence of minor and major amputations after pancreas/kidney transplantation

Received: 12 March 2002
Revised: 27 August 2002
Accepted: 17 September 2002
Published online: 10 December 2002

G. Woeste (✉) · C. Wullstein
O. Pridöhl · P. Lübke · R. Schwarz
K. Kohlhaw · W.O. Bechstein
Department of Surgery, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany
e-mail: g.woeste@em.uni-frankfurt.de
Tel.: +49-69-6301 5251
Fax: +49-69-6301 7452

Abstract Among other complications, diabetes mellitus leads to peripheral vascular disease with the risk of limb amputation. This retrospective study analyzed the incidence of amputations after simultaneous pancreas-kidney transplantation (SPK). Between June 1994 and February 2001, 200 SPKs, nine pancreas-after-kidney-(PAK) and one pancreas transplantation alone (PTA) were performed. The overall 5-year patient, pancreas-, and kidney-graft survival rates were 92.4%, 80.2% and 85.6%, respectively. Mean age at transplantation was 38.7 years, mean duration of diabetes was 26.9 years, mean duration of dialysis was 26.7 months. Nineteen (9.5%) patients after SPK (seven female/12 male) underwent 33 amputations, on average 18.7 months after transplantation. Longer duration of dialysis and a previous history of amputation were significant risk factors for an amputation after SPK ($P=0.014$, $P<0.001$). Thus, early referral for SPK before dialysis initiation may be beneficial in preventing amputation.

Keywords Pancreas · Kidney Transplantation · Amputation Dialysis

Introduction

Simultaneous pancreas-kidney transplantation (SPK) is a life-saving treatment for patients with diabetes mellitus type 1 and end-stage renal disease. The goal of this therapy is to improve quality of life and patient survival. Although successful pancreas transplantation results in euglycemia, the impact on long-term complications of diabetes is less clear [3]. A positive effect on diabetic retinopathy and peripheral neuropathy following SPK has been shown by several studies [2, 8, 9, 13, 23, 25]. Diabetes type 1 is also known to be a severe risk factor for micro- and macroangiopathy, which may, at an advanced stage of peripheral vascular disease (PVD), lead to amputation even in the young diabetic. The risk of amputation is described to be 10 to 20 times higher in diabetics than in non-diabetics [5, 19]. Several small series have reported an incidence of amputation after successful SPK raging from 10%–23% [7, 11, 17]. A larger series from the University of Wisconsin showed a 19% incidence of lower extremity amputation [15]. To investigate the effect of SPK on the clinical manifestations of diabetic vasculopathy we retrospectively analyzed the incidence of amputations in our series.

Patients and methods

Between June 1994 and August 2001, 200 SPKs, nine pancreas-after-kidney (PAK), and one pancreas transplantation alone (PTA) were performed at our institution. All PAKs were performed after primary SPK with subsequent pancreas allograft loss, thus we investigated a total of 200 patients with primary SPK. All patients undergoing SPK suffered from diabetes type 1 with diabetic nephropathy.

Antibody induction therapy with anti-thymocyte globulin (ATG) was adopted in all cases, either for 10 days ($n=36$) or single-shot intra-operatively ($n=164$); further, 32 patients additionally

Table 1 Demographics (means ± SD)

Parameter	SPK ($n=200$)
Female/ male	88/112
Age (years)	38.6±7.3
Follow up (months)	40.9±23.1
Duration of diabetes (years)	27.6±7.3
Duration of dialysis (months)	25.1 + 25.6

Table 2 Amputations prior to and after SPK

Parameter	Amputations prior to SPK	Amputations after SPK
Number of amputations	18	33
Number of patients	13/200	19/200
Incidence of amputations	6.5%	9.5%
Female/male	7/6	7/12
Months after SPK (mean ± SD)		18.7±17.8

underwent IL-2 antibody induction (daclizumab). Long-term immunosuppression was achieved with cyclosporine A (CsA), azathioprine (AZA) and prednisone (PRED) ($n=36$); CsA, mycophenolate mofetil (MMF) and PRED ($n=46$); or tacrolimus (TAC), MMF and PRED ($n=118$). Venous drainage of the pancreas graft was systemic (SV) in 184/200 (92%) cases and portal venous (PV) in 16/200 (8%). Pancreatic fluid was drained into the bladder (bladder drainage, BD) in 48 patients, and into the jejunum (enteric drainage, ED) in 152 patients.

Amputation being the severest outcome of PVD in type 1 diabetes, we focused on this event. Major amputation was defined as through, or proximal to, the tarsometatarsal joint, and a minor amputation as one distal to this joint. Upper extremity amputations were included as well, taking the wrist as the dividing line between major and minor amputations. Mean age at transplantation was 38.6±7.3 years (range 21–61 years), mean duration of diabetes type 1 was 27.6±7.3 years (range 11–49 years), mean duration of dialysis was 25.1±25.6 months (range 0–216 months.). The mean observation period was 40.9±23.1 months (range 0.4–87.4 months); 49 patients were observed for at least 5 years, 166 for at least 1 year (Table 1).

Kaplan Meier analysis was used to calculate graft and patient survival of the amputation/no amputation group. Log-rank tests were used to investigate for statistically significant differences between survival curves of both groups. Student's *t*-test and Pearson's chi-square (χ^2) test were used for univariate analysis. A P value below 0.05 was considered to be statistically significant. Statistical analysis was performed with the SPSS statistical software package (SPSS for Windows release 10.0, SPSS, Chicago, Ill.).

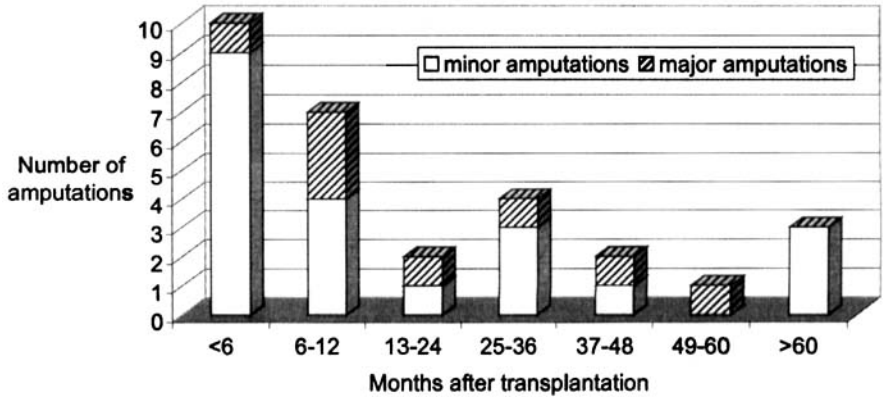
Results

Pancreas graft function was defined as near-normal blood glucose without insulin substitution, and kidney graft function was defined as freedom from dialysis. The overall patient, pancreas, and kidney survival rates were, respectively, 95.6%, 86.7%, 95.3% at 1 year, and 92.4% and 80.2%, 85.6% at 5 years. A total of 13/200 patients (6.5%) underwent 18 amputations (13 minor, five major) prior to transplantation. Eight patients underwent one amputation and five patients two amputations. After SPK 33 amputations (23 minor, ten major) were performed in 19/200 patients (9.5%). There were 1.7 times more men than women afflicted by amputation, but this difference did not show any significance ($P=0.51$, χ^2 test). Amputations after SPK were indicated at a mean time after transplantation of 18.7±17.8 months (range 1.0–66.5 months) (Table 2). Minor or major amputations were necessary at 18.3±20.4 months (range 1.4–66.5 months) and 18.8±16.8 months (range 1.0–52.9 months), respectively. The time sequence of amputations following SPK, however, varies widely (Fig. 1).

Among the patients who underwent amputation following SPK, two had suffered loss of kidney graft function before. A total of four amputations was necessary in these two patients: one patient had two minor amputations, the other had one minor and one major amputation, where the minor amputation was carried out while the kidney graft was still functioning. Kidney graft failure was not shown to be a risk factor for amputation following SPK ($P=0.98$, χ^2 test).

There was no uniform, standardized, invasive screening for PVD before the patients were listed for SPK. Prior to transplantation, 7/200 patients underwent nine interventions for peripheral artery disease (six

Fig. 1 Time after amputation



angioplasties (PTA), three bypasses). After successful transplantation, 6/200 patients needed seven vascular interventions, five PTAs and two thrombendarterectomies (TEAs). During transplantation in 6/200 patients seven vascular procedures were performed, six TEAs in five patients and one donor vascular graft interposition. Whether or not a patient underwent any kind of vascular intervention did not affect the risk for amputation following transplantation: four patients who had had previous vascular intervention underwent amputation after SPK ($P=0.097$).

Concerning other signs of vascular disease such as coronary artery disease, we retrospectively investigated again the need for intervention prior to transplantation. Twenty-one percutaneous transluminal coronary angioplasties (PTCA) were performed in 17 patients (two had two PTCAs, and one had three); in seven of those patients, eight stents were placed. Eight patients needed ten coronary artery bypass grafts (CABGs). There was no significant difference between PTCA, PTCA + stent or CABG, with amputation prior to or following SPK ($P=0.34$, 0.48, 0.45, 0.08, 0.78, 0.31, χ^2 test).

Risk factors for amputation following SPK were investigated in a univariate analysis and included age at transplantation, duration of dialysis and diabetes, type of calcineurin inhibitor and type of venous drainage. Significant risk factors for amputation after SPK were a previous history of amputation ($P<0.001$, χ^2 test) and duration of dialysis ($P=0.01$, Student's t-test) (Table 3).

There was no correlation between the incidence of amputation and the type of exocrine drainage: 7/48 patients with BD and 12/152 with ED underwent amputation following SPK ($P=0.27$, χ^2 test). There was no difference in patient, pancreas- and kidney-graft survival rates when patients with and without amputation after SPK were compared (Table 4).

Table 3 Risk factors for amputation (means ± SD)

Factor	Amputation $n=19$	No amputation $n=181$	P
H/o amputation	6	7	<0.001[a]
Duration of dialysis (months)	38.8±51.4	23.7±21.0	0.01[b]
Duration of diabetes (years)	29.0±6.9	27.4±7.3	0.36[b]
Female/male	7/12	81/100	0.51[a]
SV/PV	18/1	166/15	0.64[a]
Age (years)	38.7±8.1	38.5±7.2	0.92[b]
TAC/CsA	12/7	106/75	0.82[a]

[a]Pearson's χ^2 test
[b]Student's t-test

Table 4 Five-year survival, analyzed by log-rank test

Parameter	Amputation $n=19$	No amputation $n=181$	P
Patient survival	93.3%	93.2%	0.86
Pancreas graft survival	84.2%	81.7%	0.89
Kidney graft survival	86.1%	85.2%	0.82

Discussion

Successful pancreas-kidney transplantation restores normoglycemia and thus may improve long-term diabetic complications. Several studies have shown that SPK is a life-saving procedure for patients with diabetes and end-stage renal failure [3, 4, 16, 21]. Compared with diabetic patients with kidney transplants alone or with failed pancreas grafts, patients with functioning pancreas grafts showed substantially higher survival rates [20, 24]. Presumably, the decrease in mortality results from the beneficial effect of long-term normoglycemia on diabetic late complications. The 5-year patient, pancreas- and kidney-graft survival rates in our series are 92.4%, 80.2%, and 85.6%, respectively. This is comparable to other centers' experience [22].

In this study we analyzed the incidence of amputations following SPK. The overall incidence of minor and major amputations in our series was 9.5%. The cumulative risk of amputation in diabetic patients with exogenous insulin is described in the literature as being approximately 10%–11% [12, 14, 19]. Compared with these published data, our data showed that the risk of amputation in our series was slightly lower. In our group, there were 1.7 times more male patients afflicted than female patients. As shown in other studies, male gender predicts amputation [12, 18, 19]. One explanation for the high correlation between male gender and amputation might be the lower level of foot-care than that in female patients [12]. It may also be a result of different occupational and recreational activities that put more stress on the feet [19]. Also, men may visit a physician later than women do in cases of any foot complaints [12, 19]. The reasons for the necessity of amputation are complex. Concerning diabetic patients, strong associations were found between amputation and other diabetic complications, such as retinopathy and peripheral neuropathy [10, 12].

Multiple mechanisms contribute to the development of diabetic foot ulcer, which may lead to amputation. Several studies have shown that peripheral sensory neuropathy and PVD are independent risk factors for lower extremity amputation in patients with diabetes [1, 6, 12]. Peripheral sensory neuropathy and the resulting abnormal toe and foot postures and reduced sensation predispose the feet to trauma, and with disturbed circulation, the healing of the lesions is delayed. The distinction between neuropathic and vascular ulcers is sometimes not a clear one, because neuropathy may

contribute to foot ulceration via effects on the microcirculation [1].

Duration of diabetes is presumed to be a risk factor for amputation [6, 19]. In our series there was no significant difference in duration of diabetes between amputees and non-amputees. A previous history of amputation, however, was a significant risk factor for amputation following SPK. Furthermore, and perhaps surprisingly, duration of dialysis was also a significant risk factor for amputation following SPK. On the one hand, this is another indicator for advanced diabetic complications after long-standing diabetic nephropathy. On the other hand, dialysis itself may be a risk factor for accelerated progression of vascular disease.

In summary, the duration of dialysis and a previous history of amputation in diabetic patients were identified as risk factors for amputation following SPK, which can mean a very severe physical handicap for the afflicted patients. These findings lead to the conclusion that type 1 diabetics with end-stage renal disease should be evaluated for SPK as soon as renal function deteriorates. Further studies should be carried out, in a larger series, to determine whether early SPK transplants can reduce the incidence of amputations after SPK.

References

1. Adler AI, Boyko EJ, Ahroni JH, Smith DG (1999) Lower-extremity amputation in diabetes. Diabetes Care 22:1029–1035
2. Allen RD, Al-Harbi IS, Morris JG, Clouston PD, O'Connell PJ, Chapman JR, Nankivell BJ (1997) Diabetic neuropathy after pancreas transplantation: determinants of recovery. Transplantation 63:830–838
3. Bechstein WO (2001) Long-term outcome of pancreas transplantation. Transplant Proc 33:1652–1654
4. Becker BN, Brazy PC, Becker YT, Odorico JS, Pintar Ti, Collins BH, Pirsch JD, Leverson GE, Heisey DM, Sollinger HW (2000) Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. Kidney Int 57:2129–2135
5. Bild DE, Selby JV, Sinnock P, Browner WS, Bravernan P, Showstack JA (1989) Lower extremity amputation in people with diabetes: epidemiology and prevention. Diabetes Care 12:24–31
6. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG (1999) A prospective study of risk factors for diabetic foot ulcer. Diabetes Care 22:1036–1042
7. Bruce DS, Newell KA, Josephson MA, Woodle ES, Piper JB, Millis JM, Seaman DS, Carnrike CL Jr, Huss E, Thistlethwaite JR Jr (1996) Long-term outcome of kidney/pancreas transplant recipients with good graft function at one year. Transplantation 62:451–456
8. Cashion AK, Hathaway DK, Milstead EJ, Reed L, Gaber AO (1999) Changes in patterns of 24-hr heart rate variability after kidney and kidney-pancreas transplant. Transplantation 68:1846–1850
9. Chow VC, Pai RP, Chapman JR, O'Connell PJ, Allen RD, Mitchell P, Nankivell BJ (1999) Diabetic retinopathy after combined kidney-pancreas transplantation. Clin Transplant 13:356–362
10. Coppini DV, Young PJ, Wenig C, MacLeod AF, SûÑnksen PH (1998) Outcome of diabetic foot complications in relation to clinical examination and quantitative sensory testing: a case-control study. Diabet Med 15:765–771
11. Cosimi AB, Auchincloss H Jr, Delmonico FL, Fang L, Nathan DM, Tolkoff-Rubin N, Rubin RH, Yang HC, Russell PS (1988) Combined kidney and pancreas transplantation in diabetics. Arch Surg 123:621–625
12. Hû\'flmû\'fllû\'flinen H, RûÑnnemaa T, Halonen J-P, Toikka T (1999) Factors predicting lower extremity amputations in patients with type 1 or type 2 diabetes mellitus: a population-based 7-year follow-up study. J Intern Med 246:97–103
13. Hathaway DK, Abell T, Cardoso S, Hartwig MS, el Gebely S, Gaber AO (1994) Improvement in autonomic and gastric function following pancreas-kidney versus kidney-alone transplantation and the correlation with quality of life. Transplantation 57:816–822
14. Humphrey LL, Palumbo PJ, Butters MA, Hallett JW Jr, Chu CP, O'Fallon WM, Ballard DJ (1994) The contribution of non-insulin-dependent diabetes to lower-extremity amputation in the community. Arch Intern Med 154:885–892
15. Kalker AJ, Pirsch JD, Heisey D, Sollinger HW, Belzer FO, Knechtle SJ, D'Alessandro AM (1996) Foot problems in the diabetic transplant recipient. Clin Transplant 10:503–510
16. Landgraf R (1996) Impact of pancreas transplantation on diabetic secondary complications and quality of life. Diabetologia 39:1415–1424
17. Morrissey PE, Shaffer D, Monaco AP, Conway P, Madras PN (1997) Peripheral vascular disease after kidney-pancreas transplantation in diabetic patients with end-stage renal disease. Arch Surg 132:358-362
18. Moss SE, Klein R, Klein BE (1996) Long-term incidence of lower extremity amputation in a diabetic population. Arch Fam Med 5:391–398
19. Moss SE, Klein R, Klein BEK (1999) The 14-year incidence of lower extremity amputations in a diabetic population. Diabetes Care 22:951–959
20. Ojo AO, Meier-Kriesche H-U, Hanson JA, Leichtman A, Magee JC, Cibrik D, Wolfe RA, Port FK, Agodoa L, Kaufman DB, Kaplan B (2001) The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. Transplantation 71:82–90
21. Smets YF, Westendorp RG, van der Pijl JW, de Charro FT, Ringers J, de Fijter JW, Lemkes HH (1999) Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes mellitus and end-stage renal failure. Lancet 353:1915–1919
22. Sollinger HW, Odorico JS, Knechtle SJ, D'Alessandro AM, Kalayoglu M, Pirsch JD (1998) Experience with 500 simultaneous pancreas-kidney transplants. Ann Surg 228:284–296
23. Sosna T, Saudek F, Dominek Z (1998) Effect of successful combined renal and pancreatic transplantation on diabetic retinopathy. Acta Univ Palacki Olomuc Fac Med 141:75–77

24. Tyden G, Tollemar J, Bolinder J (2000) Combined pancreas and kidney transplantation improves survival of patients with end-stage diabetic nephropathy. Clin Transplant 14:505–508

25. Ulbig M, Kampik A, Thurau S, Landgraf R, Land W (1991) Long-term follow-up of diabetic retinopathy for up to 71 months after combined renal and pancreatic transplantation. Graefes Arch Clin Exp Ophthalmol 229:242–245