Pancreas after Kidney Transplants in Posturemic Patients with Type I Diabetes Mellitus

ANGELIKA C. GRUESSNER, DAVID E. R. SUTHERLAND, DAVID L. DUNN, JOHN S. NAJARIAN, ABHI HUMAR, RAJA KANDASWAMY, and RAINER W. G. GRUESSNER

Department of Surgery, University of Minnesota, Minneapolis, Minnesota.

Abstract. Pancreas after previous kidney (PAK) transplants are an attractive option for type 1 diabetic patients because of the short waiting time and use of living kidney donors. Factors associated with the increased success rate of PAK transplants in four immunosuppressive eras were analyzed. Between July 1, 1978, and April 30, 2000, 406 PAK transplants were performed in posturemic patients. Four immunosuppressive eras were analyzed: (1) the precyclosporine era, era 1 (n = 65; 16%); (2) the cyclosporine era, era 2 (n = 109; 27%); (3) the tacrolimus era with monoclonal or polyclonal antibody induction therapy, era 3 (n = 104; 26%); and (4) the tacrolimus era with monoclonal and polyclonal antibody induction therapy, era 4 (n = 128; 31%). Patient and graft survival, rejection, and technical failure rates were calculated. Patient survival rates have remained high over time, from 91% (era 1) to 96% (era 4) at 1 yr posttransplant. Pancreas graft survival rates with primary cadaver transplants have significantly increased, from 17% (era 1) to 81% (era 4) at 1 yr. The rate of graft loss from rejection has significantly decreased, from 78% (era 1) to 9% (era 4) at 1 yr. Results were best when donors and recipients were matched for at least one antigen per HLA locus. Kidney graft survival was higher in PAK transplant recipients compared with diabetic recipients of kidney transplants alone from the time of the kidney as well as the pancreas transplants. PAK recipients now enjoy >80% graft survival at 1 yr. This improvement in outcome results from better immunosuppression, good matching, and close posttransplant monitoring for rejection.

According to the International Pancreas Transplant Registry, 17% of all pancreas transplants in the United States in 1999 (1) were pancreas after previous kidney (PAK) transplants in posturemic patients. Although the number of PAK transplants has significantly increased over time, they still account for only 10% of all pancreas transplants ever performed. Most pancreas transplants in the United States (76% in 1999) are still done simultaneously with a kidney transplant (SPK) in uremic patients (1). The third and smallest pancreas transplant category is pancreas transplants alone (PTAs) in nonuremic patients.

Until the mid-1990s, the results of solitary pancreas transplants (PAK and PTA) had trailed those of the SPK category. We recently reported our single-center PTA results in nonuremic patients with extremely labile insulin-dependent diabetes mellitus (IDDM) and demonstrated that a graft survival rate of 80% at 1 yr can be achieved with tacrolimus (TAC) and mycophenolate mofetil (MMF)–based immunosuppression (2).

PAK transplants are an attractive option for IDDM patients who have already undergone a kidney transplant. At our center, many IDDM patients decided to initially undergo a living kidney transplant alone (KTA), both because of better long-term graft survival compared with a cadaver KTA and because dialysis could be pre-empted or shortened. Other patients underwent a cadaver KTA at a time when SPK transplants were not yet an option. These KTA recipients were already committed to immunosuppression because of their kidney transplant, so a subsequently transplanted pancreas corrected their metabolic control problem, made them insulin-independent as well as dialysis-free, stopped the progression of secondary complications of diabetes, and protected their transplanted kidney from (recurrence of) diabetic nephropathy.

At the University of Minnesota, we have done more than 400 pancreas transplants in posturemic patients who had previously undergone a kidney transplant. They account for more than one third of all pancreas transplants performed at our center. As shown in this analysis, the current high success rate of PAK transplants warrants more widespread application.

Materials and Methods

Study Population

Of 1182 pancreas transplants at the University of Minnesota between July 1, 1978, and April 30, 2000, 406 (34%) were PAK transplants. The number of PAK transplants significantly increased between 1996 (n = 28) and 1999 (n = 66).

All 406 PAK recipients had undergone at least one previous kidney transplant: in 284 (70%), a living kidney donor (LD) was used; in 122 (30%), a cadaver donor (CAD). In all, 381 (94%) of these previous kidney transplants were primary kidney transplants (274 LD, 107 CAD); 23 (6%), second kidney transplants (10 LD, 13 CAD); 1, a
third kidney transplant (CAD); and 1, a fourth kidney transplant (CAD).

Of the 406 pancreas transplants, CAD donors were used in 374 (92%); LD, in 32 (8%). Of the recipients, 195 (48%) were women and 211 (52%) men.

In all of these 406 pancreas transplants, 310 (279 CAD, 31 LD) (76%) were primary pancreas transplants; 80 (79 CAD, 1 LD) (20%), second pancreas transplants; 13 (3%), third pancreas transplants; and 3 (1%) fourth pancreas transplants. Of the 80 second pancreas transplant recipients, 36 (45%) had previously undergone SPK and 44 (55%) PAK transplants. Of the 310 primary pancreas transplant recipients, 36 (37%); LD, in 32 (8%). Of the recipients, 195 (48%) were women and 211 (52%) men.

We analyzed results in four different immunosuppressive eras:

Era 1, the precyclosporine (pre-CSA) era ($n = 65$; 16%)
Era 2, the CSA era ($n = 109$; 27%)
Era 3, the TAC era with monoclonal or polyclonal antibody induction therapy ($n = 104$; 26%)
Era 4, the TAC era with monoclonal and polyclonal antibody induction therapy ($n = 128$; 31%).

Recipient age at the time of the pancreas transplant increased significantly over time, from 33 ± 6 yr (range, 21 to 46 yr) in era 1 to 41 ± 8 yr (range, 20 to 64 yr) in era 4 (Figure 1). LD pancreas transplant recipients increased significantly over time (28% in era 1, 12% in era 2, 1% in era 3, 0% in era 4), while at the same time the number of LD transplants in the SPK category increased (3). The proportion of retransplants increased over time, from 18% in era 1 to 24% in era 4. No differences between the four eras were noted in gender distribution, mean age at diagnosis of IDDM, or mean duration of IDDM.

The most common technique to manage pancreas exocrine secretions was bladder drainage, followed by enteric drainage, duct injection, and open drainage. In era 1, bladder drainage was not used; 43% of pancreas transplants were duct-injected and 29% were enteric-drained. In era 2, 94% of pancreas transplants were bladder-drained; in era 3, 93%. In era 4, 88% were bladder-drained and 12% enteric-drained.

In eras 3 and 4, information was available at the time of the pancreas transplant on the presence of vascular disease: 14% of the recipients had had a previous myocardial infarction, 10% had undergone a coronary bypass procedure, 3.4% had had a stroke, 1.5% had had a transient ischemic attack, 2% had undergone a noncoronary bypass procedure, 2.5% had had major (leg or arm) amputations, and 8.8% had had minor (toes or fingers) amputations. Recipients with vascular disease were significantly older than those without (44 ± 8 versus 37 ± 6 yr).

Donor and recipient selection criteria, donor and recipient transplant procedures, perioperative care, general postoperative care, and antimicrobial prophylaxis and therapy have been detailed elsewhere (4–6).

**Immunosuppression**

In era 1, only azathioprine and prednisone were used for induction and maintenance immunosuppression. Only one recipient received antibody therapy (Minnesota ALG).

In era 2, CSA was added for induction and maintenance therapy; all recipients received antibody therapy for induction. Polyclonal antibody induction therapy (Minnesota ALG or ATGAM) was used in 88% and monoclonal antibody therapy (OKT3) in 12% of recipients. Since era 2, quadruple-drug therapy has been used predominantly for induction and triple-drug therapy for maintenance immunosuppression. The median duration of antibody therapy in era 2 was 13 d.

In era 3, TAC was used in combination with prednisone and, initially, azathioprine (22%); MMF (78%), once it was approved by the federal Food and Drug Administration, replaced azathioprine. Although outcome seemed to be slightly more favorable with MMF, there were no significant differences at 1 yr. For induction, polyclonal antibody therapy (ATGAM) was used in 99% and monoclonal antibody therapy (OKT3) only in 1% of recipients. The median duration of antibody therapy was 5 d.

In era 4, TAC, MMF, and prednisone remained the principal maintenance immunosuppressants; occasionally, MMF was replaced by rapamycin ($n = 4$) during the initial hospital stay. For induction, a new monoclonal antibody (interleukin-2 receptor blocker, daclizumab) was used (1 mg/kg intravenous), either alone (21%) or in combination (79%) with a polyclonal antibody (ATGAM or thymoglobulin). The median duration of antibody therapy was 3 d.

The median duration of antibody therapy decreased significantly from era 2 to era 4. Only in era 4 were monoclonal and polyclonal antibodies given in combination as standard induction therapy.

In era 2, CSA levels were adjusted to achieve whole blood levels of 200 to 250 ng/ml for the first 6 mo, 150 to 200 ng/ml for the second 6 mo, and 100 to 150 ng/ml thereafter, using high-pressure liquid chromatography. In eras 3 and 4, TAC levels were adjusted to achieve whole blood levels of 8 to 13 ng/ml for the first 6 mo and 5 to 10 ng/ml thereafter.

**HLA Matching**

For HLA typing, the nylon-column separation technique was initially used for class I and class II antigens; since 1989, the immunomagnetic beams technique has been used for class I antigens and DNA typing for class II antigens. Our computation of HLA matches followed United Network for Organ Sharing policy 3A (November 1998) for split equivalences.

**Diagnosis and Treatment of Rejection**

In bladder-drained pancreas transplants, rejection has been defined by a decrease of urinary amylase levels of ≥25% from baseline on
two consecutive measurements or by biopsy diagnosis (open biopsies in era 1; open or transcystoscopic biopsies in era 2; percutaneous, laparoscopic, or transcystoscopic biopsies in eras 3 and 4) (7). In enteric-drained or duct-injected pancreas transplants, rejection has been defined by an increase in serum glucose, serum amylase, or lipase levels, or by biopsy diagnosis. Pancreas rejection episodes were treated with a 7-d course of anti–T cell therapy and by recycling of a steroid taper.

Statistical Analyses

For univariate data analysis, categorical variables were analyzed using the $\chi^2$ test and, when applicable, Fisher’s exact test. Continuous variables were analyzed parametrically using the $t$ test and nonparametrically using the Kruskal-Wallis test. Graft and patient survival rates were calculated according to Kaplan-Meier. The time of pancreas graft loss was determined by return to exogenous insulin use after insulin independence. Kidney failure was defined by the need for dialysis or a retransplant. Kidney graft function was followed independently. Vascular disease included a previous history of peripheral bypass surgery; stroke or transient ischemic attack; or coronary artery bypass, coronary angioplasty, and/or myocardial infarction. For all univariate statistical tests, $P < 0.05$ defined significance. When we analyzed all cases, death with a functioning graft was considered a graft failure. However, when we analyzed immunologic graft failure, technical failures were excluded and death with a functioning graft cases were censored.

For multivariate analysis, we studied only eras 3 and 4. We excluded era 1 because of its imperfect HLA-typing techniques, incomplete patient information, and less frequent use of biopsy for the diagnosis of rejection. We excluded era 2 because of its incomplete information on recipients’ vascular risk factors, which had a significant effect on graft and patient survival. In addition, we studied the following variables: HLA typing (separate analyses for HLA A, B, and DR loci), shared matches with the donor kidney, donor age ($\leq 45$ versus $> 45$ yr), recipient age ($\leq 45$ versus $> 45$ yr), pancreas transplant number (retransplant versus primary), kidney transplant number before the pancreas transplant (retransplant versus primary), body mass index ($\leq 25$ versus $> 25$ kg/m$^2$ at time of transplant), type of antibody induction therapy (monoclonal versus polyclonal), cytomegalovirus infection during the first 3 mo posttransplant, pancreas preservation time ($\leq 20$ versus $> 20$ h), and donor cause of death (traumatic versus nontraumatic). For multivariate analysis, $P < 0.2$ was considered noticeable.

Results

Patient Survival

Overall patient survival rates (CAD and LD) at 1 and 3 yr in era 1 were 91% and 83%; in era 2, 93% and 84%; in era 3, 97% and 90%, respectively. The rate at 1 yr in era 4 was 96%; the rate at 3 yr was not available at the time of this writing because of the short follow-up time (Figure 2). The difference between the four eras was statistically significant ($P < 0.049$).

Patient survival rates for CAD recipients at 1 and 3 yr in era 1 were 89% and 81%; in era 2, 92% and 83%; in era 3, 97% and 90%, respectively. The rate at 1 yr in era 4 was 96%; the rate at 3 yr was not available at the time of this writing because of the short follow-up time. The differences between the four eras was statistically significant ($P \leq 0.02$). We noted no further improvement in era 4 over era 3 ($P \geq 0.74$).

Patient survival rates for LD pancreas recipients at 1 and 3 yr in era 1 were 94% and 88%; in era 2, 100% and 100%, respectively ($P \geq 0.3$). In eras 3 and 4, only 1 such transplant was done; the recipient was alive 41 mo posttransplant.

Patient survival rates for older CAD pancreas recipients (>45 yr) significantly improved over time ($P < 0.05$). For that reason, the number of older recipients increased from 2% in era 1 to 27% in era 4. In era 1, all but 1 recipient was $\leq 45$ yr. In era 2, patient survival rates at 1 and 3 yr were 95% and 86% for recipients $\leq 45$ yr and 73% and 67% for recipients $> 45$ yr, respectively; the difference was not significant ($P \geq 0.06$). In era 3, patient survival rates at 1 and 3 yr were 97% and 93% for recipients $\leq 45$ yr and 96% and 84% for recipients $> 45$ yr of age, respectively ($P \geq 0.1$). In era 4, the rate at 1 yr was 96% for recipients $\leq 45$ yr and 97% for recipients $> 45$ yr ($P \geq 0.7$).

In eras 3 and 4, patient survival rates were not different for recipients without versus with vascular disease (this information was not available for eras 1 and 2). At 1 and 3 yr, patient survival rates were 99% and 92% for recipients without vascular disease and 96% and 90%, respectively, for those with ($P \geq 0.3$).

Pancreas Graft Survival

Overall pancreas graft survival rates (CAD and LD) at 1 and 3 yr in era 1 were 28% and 25%; in era 2, 47% and 34%; in era 3, 78% and 60%, respectively. The rate in era 4 at 1 yr was 77%; the rate at 3 yr was not available at the time of this writing because of the short follow-up time (Figure 3). The difference between the four eras was statistically significant ($P \leq 0.0001$).

Pancreas graft survival rates for CAD recipients at 1 and 3 yr in era 1 were 19% and 17%; in era 2, 48% and 33%; in era 3, 78% and 60%, respectively. The rate in era 4 at 1 yr was 77%; the rate at 3 yr was not available at the time of this writing because of the short follow-up time. The difference between the four eras was statistically significant ($P \leq 0.0001$); the difference between eras 3 and 4 was not ($P \geq 0.59$).

Pancreas graft survival rates for LD pancreas recipients at 1 and 3 yr in era 1 were 50% and 44%; in era 2, 38% and 38%,
Graft survival by era.

Pancreas Graft Loss from Rejection

When we analyzed only technically successful pancreas transplants, the overall pancreas graft loss rates from rejection (CAD and LD) at 1 and 3 yr in era 1 were 59% and 64%; in era 2, 28% and 41%; in era 3, 10% and 19%, respectively. The rate in era 4 at 1 yr was 9%; the rate at 3 yr was not available at the time of this writing because of the short follow-up time (Figure 4). The difference between the four eras was statistically significant (P < 0.0001), although one has to remember that biopsies were less frequently done in eras 1 and 2 as compared with eras 3 and 4.

The CAD pancreas graft loss rates from rejection at 1 and 3 yr in era 1 were 75% and 78%; in era 2, 27% and 43%; in era 3, 11% and 19%, respectively. The rate in era 4 at 1 yr was 9%. The difference between the four eras was statistically significant (P ≤ 0.0001).

The LD pancreas graft loss rates from rejection at 1 and 3 yr in era 1 were 10% and 20%; in era 2, 29% and 29%, respectively. The difference was not statistically significant (P ≥ 0.8).

For CAD pancreas transplants only, we compared graft loss from rejection at 1 and 3 yr for primary and retransplant recipients. The rates in era 1 were 78% and 82% (primary) and 67% and 67% (retransplants), respectively; in era 2, 18% and 35% (primary) and 47% and 61% (retransplants), respectively (P = 0.09); in era 3, 12% and 20% (primary) and 6% and 13% (retransplants), respectively (P = 0.6). The rate at 1 yr in era 4 was 6% (primary) and 19% (retransplants) (P = 0.08). The difference between the four eras was statistically significant both for primary transplants (P ≤ 0.0001) and for retransplants (P ≤ 0.0002).

Pancreas Rejection Episodes

The rates of first reversible rejection episodes at 1 and 3 yr for pancreas recipients only were not recorded in era 1. The rates in era 2 (only technically successful cases) were 53% and 50%, respectively, for those with vascular disease (P ≤ 0.043).
54% (primary) and 59% and 75% (retransplants); in era 3, 43% and 52% (primary) and 38% and 38% (retransplants), respectively. The rate in era 4 was 51% (primary) and 47% (retransplants) (Figure 5). The difference between the three eras was statistically significant only for retransplants ($P < 0.05$).

The rate of first rejection episodes at 1 yr in eras 3 and 4 combined, according to the type of induction therapy, was as follows: for polyclonal induction therapy only, 42%; for monoclonal induction therapy only, 36%; for combined monoclonal and polyclonal induction therapy, 59% (Figure 6). The difference was statistically significant ($P < 0.05$).

**Pancreas Graft Loss from Technical Failures**

The technical failure rate improved over time. For CAD pancreas transplants only, the rate in era 1 was 21%; in era 2, 25%; in era 3, 16%; in era 4, 10%. The difference between the four eras was statistically significant ($P = 0.02$). For LD pancreas transplants only, the technical failure rate in era 1 was 39%; in era 2, 46%. The difference was not statistically significant ($P = 0.5$). The most common causes of technical failures ($n = 63$ in CAD grafts, $n = 13$ in LD grafts) are provided in Table 1.

The rate of graft thrombosis has significantly decreased, from 10% in era 2 and 12% in era 3 to only 5% in era 4. The rate of graft failures caused by infection was 14% in era 1, 5% in era 2, 2% in era 3, and 0% in era 4.

The rate of graft loss from technical failure was 7.9% if the interval between the kidney and pancreas transplant was ≤2 mo; 18% if >2 to ≤12 mo; and 21% if >12 mo.

**HLA Typing**

The effect of HLA A, B, and DR matching on pancreas graft survival decreased over time (era 2 > era 3 > era 4) and is directly associated with the immunosuppressive regimen (CSA > TAC).

At our center, we have attempted to match the new pancreas with at least one A, B, and DR antigen; we have also tried to avoid a totally mismatched locus.

In era 2, graft survival rates at 1 yr for bladder-drained transplants were 37% with at least 1 mismatched locus versus 59% with at least 1 match per A, B, and DR locus; at 3 yr, the difference was 24% versus 40% ($P < 0.05$).

In era 3, graft survival rates at 1 yr were 74% with at least 1 mismatched locus versus 84% with at least 1 match per locus ($P = 0.66$). In era 4, graft survival rates at 1 yr were 78% and 77%.

The effect of HLA matching was stronger for retransplants than for primary transplants. For bladder-drained retransplants, the overall graft survival rates at 1 and 3 yr in the group with at least 1 mismatched locus were 48% and 29% versus 63% and 40%, respectively, in the group with at least 1 match per locus ($P = 0.03$).

Regarding graft loss from rejection, the matching effect was most striking in era 2: graft loss rates at 1 and 3 yr were 41% and 48% with at least 1 mismatched locus ($n = 37$) versus 9% and 37% with at least 1 match per locus ($n = 33$) ($P = 0.09$), respectively. In era 3, graft loss rates from rejection at 1 yr were 13% with at least 1 mismatched locus ($n = 38$) versus 9% with at least 1 match per locus ($n = 44$).

In pancreas transplantation, the PAK category is unique: the previously transplanted kidney graft is functioning and its set of antigens, for which possible tolerance is already expressed, increases the pool of recipient antigens. Using our above-mentioned proposal for at least one match per locus, we increased the pool of suitable matched donors without a decrease

Table 1. Causes of pancreas graft loss from technical failures

<table>
<thead>
<tr>
<th>Cause</th>
<th>CAD Grafts (%)</th>
<th>LD Grafts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft thrombosis</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Infection/leak</td>
<td>31</td>
<td>46</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>13</td>
<td>8</td>
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<tr>
<td>Bleeding</td>
<td>5</td>
<td>—</td>
</tr>
</tbody>
</table>

*a CAD, cadaver donor; LD, living donor.
in outcome. In fact, one third of all recipients in the less well matched group shared antigens with the kidney and moved into the better matched category.

Taking the shared kidney antigens into account, the graft loss rates from rejection in era 2 was 45% at 1 yr with at least 1 totally mismatched locus \((n = 26)\) versus 17% with at least 1 match per locus \((n = 44)\) \((P = 0.002)\). The graft loss rate from rejection in era 3 remained 13% \((n = 24)\) for transplants with at least 1 total mismatch versus 10% \((n = 58)\) for the group with at least 1 match per locus \((P = 0.6)\).

**Time Interval between Kidney and Pancreas Transplant**

For our 406 PAK transplants, the median time interval from the kidney to pancreas transplant was 19.8 mo. The time interval was shorter for LD kidney recipients (median, 17.8 mo) than for CAD kidney recipients (median, 26.7 mo). In era 1, the median interval was 39 mo; in era 2, 18.7 mo; in era 3, 16.8 mo; and in era 4, 12.0 mo \((P = 0.01)\).

**Kidney Graft Survival after Pancreas Transplantation**

Kidney graft survival rates at 1 and 3 yr after the pancreas transplant in era 1 were 88% and 78%; in era 2, 93% and 82%; in era 3, 94% and 80%, respectively. In era 4, the kidney graft survival rate was 94% at 1 yr after the pancreas transplant; the rate at 3 yr was not available at the time of this writing because of the short follow-up time. The difference between the four eras was statistically significant \((P \geq 0.03)\).

For CAD kidney transplants only, late differences between the four eras reached statistical significance using the log rank test \((P = 0.01)\). When the Wilcoxon test was used for early differences, the \(P\) value was 0.18. For LD kidney transplants, we noted no significant difference between the four eras \((P \geq 0.13)\).

At the time of this analysis, 301 (74%) of the transplanted kidneys were functioning; graft failure was reported in 38 (10%) recipients, and 66 (16%) recipients had died with a functioning kidney graft. The most common cause of graft failure was chronic or acute rejection, accounting for 73% of all kidney graft failures.

**Kidney Graft Survival: PAK versus KTA**

This analysis was on the basis of a comparison of outcomes between PAK and diabetic KTA recipients at our institution during the same time period. The differences in immunosuppression between the two groups were: (1) an additional course of induction therapy at the time of the pancreas transplant in the PAK group and (2) antirejection treatment in case of pancreas rejection episodes. CSA and PAK long-term maintenance levels did not differ between the groups. Demographically, both groups were similar with the exception of recipient age: on average, recipients in the KTA group were 4 yr older.
Kidney Graft Survival after the Kidney Transplant (PAK and KTA).

Kidney graft survival rates at 1 and 3 yr after the kidney transplant were higher in the PAK (versus KTA) category in all four eras. The difference between the two categories was statistically significant for eras 2, 3, and 4 (Figure 7A).

Kidney Graft Survival from Time of Kidney (KTA) versus Pancreas Transplant (PAK). Even when the interval between the kidney and pancreas transplant in the PAK category was disregarded, early kidney graft survival remained significantly higher in the PAK versus KTA categories in eras 3 and 4 (Figure 7B).

Our analysis, according to the kidney donor source (CAD versus LD), showed no difference between kidney graft survival from the time of the kidney transplant (KTA) versus pancreas transplant (PAK), except for 2 eras: in era 2, for CAD kidneys, kidney graft survival was significantly better in the PAK category, whereas in era 1, for LD kidneys, kidney graft survival was significantly higher in the KTA category.

Patient Survival: PAK versus KTA

Patient Survival after the Kidney Transplant (PAK and KTA). Patient survival rates at 1 and 3 yr after the kidney transplant were higher in the PAK (versus KTA) category in all 4 eras and reached statistical significance in both era 2 ($P = 0.004$) and eras 3 and 4 ($P = 0.002$) (Figure 8A).

Patient Survival from Time of Kidney (KTA) versus Pancreas Transplant (PAK). When we disregarded the interval between the kidney and pancreas transplant in the PAK category, patient survival rates were still higher in the PAK versus KTA category in eras 3 and 4 (Figure 8B).

Multivariate Analyses

According to our multivariate analyses, the following risk factors increased the risk of pancreas graft loss (Table 2): vascular disease at the time of the pancreas transplant, poor match on the HLA-B locus, a pancreas retransplant, a larger body mass index, and longer preservation time. The use of polyclonal antibody therapy decreased the relative risk of graft loss. The following factors did not significantly increase the risk of pancreas graft loss: older donor age, older recipient age (older patients were less prone to rejection), poor matching on the HLA-A and DR locus, shared antigens, cerebrovascular donor cause of death, monoclonal and polyclonal antibody induction therapy, and cytomegalovirus infection.

The following risk factor increased the risk of poor patient survival (Table 3): multiple kidney transplants before the pancreas transplant. The following factors did not increase the risk of poor patient survival: older donor age for the pancreas retransplant, longer preservation time, a larger body mass index, cerebrovascular donor cause of death, HLA-A and DR matching, and shared antigens.

Discussion

Our single-center analysis shows that PAK transplants can now be done almost as successfully as SPK transplants: the 1-yr primary pancreas graft survival rate is $>80\%$. This im-
provement in outcome is a result of refined surgical techniques, superior antimicrobial prophylaxis and therapy, more efficient diagnosis and treatment of rejection, and, above all, new immunosuppressive regimens. Specifically, the introduction of TAC in the mid-1990s and of MMF in the late 1990s has contributed to this improvement.

In our experience, the introduction of newer anti–T cell agents, such as the monoclonal interleukin-2 receptor blockers, has not resulted in further improvement in posttransplant outcome. TAC-based immunosuppression in this study was used in eras 3 and 4. In era 3, only polyclonal antibodies were used (median duration, 5 d); in era 4, both monoclonal and polyclonal antibodies were used (median duration, 2 to 3 d). But combining monoclonal and polyclonal antibodies in era 4 for an overall shorter antibody induction period did not increase graft survival. In contrast, the incidence of reversible rejection episodes was higher in era 4 than in era 3. Although the shorter duration of induction antibody therapy in era 4 had evolved over time and was not studied in a randomized, prospective fashion, a longer duration of antibody induction therapy seems to diminish the risk of rejection episodes in PAK recipients.

Since TAC and MMF have been used as the mainstay immunosuppressants (eras 3 and 4), the rate of graft loss from irreversible rejection has significantly decreased to ≤10% (compared with 28% in the CSA era, era 2). Although the 1-yr rate of reversible rejection episodes has also significantly decreased over time, it still remains high: 42% in era 3 and 48% in era 4 for primary transplants. Using TAC- and MMF-based immunosuppression, only one fifth of recipients with rejection episodes ultimately lost their pancreas graft to irreversible rejection. Two reasons are behind this low figure: close monitoring for rejection and liberal use of percutaneous graft biopsies, leading to early therapy (7). In bladder-drained pancreas transplants, a decrease in urinary amylase levels remains, in our experience, the simplest chemical cue to initiate a workup for rejection (8). Urinary amylase monitoring is also less invasive than protocol biopsies, as proposed for enteric-drained pancreas transplants (9). Therefore, we have continued to use bladder drainage in PAK transplants as the standard technique for monitoring pancreas exocrine secretions. If hypomyelarasia is documented, we do confirmatory pancreas graft biopsies—the gold standard for detecting graft rejection—to avoid unnecessary treatment (10). At our center, such biopsies are done percutaneously under CT guidance and have a very low complication rate and a high tissue yield rate. The disadvantage of bladder drainage is its high chronic complication rate (e.g., recurrent urinary tract infections, dehydration, and metabolic acidosis), which has resulted in a 7% and 25% conversion (from bladder to enteric drainage) rate at 1 and 3 yr in eras 3 and 4, respectively.

We also noted improvements in outcome after PAK transplants in other areas. The results for recipients >45 yr are no longer different than for those ≤45 yr. Likewise, in the TAC eras (eras 3 and 4), we no longer see a difference in outcome between primary transplants and retransplants. In fact, a retransplant is not a high-risk procedure in our hands; we routinely offer it to recipients whose primary pancreas graft fails.

LD PAK transplants were primarily done in eras 1 and 2, when the rejection rates were significantly lower for LD (versus CAD) grafts. Since the introduction of TAC, this immunologic advantage is hardly present anymore. We continue to offer segmental LD pancreas transplants after a previous kid-

### Table 2. Multivariate analysis: Risk factors for worse pancreas graft survival (eras 3 and 4)a

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P Value</th>
<th>RR</th>
</tr>
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<tbody>
<tr>
<td>Recipient age &gt;45 (versus ≤45 yr)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Pancreas retransplant</td>
<td>0.07</td>
<td>1.8</td>
</tr>
<tr>
<td>Kidney retransplant</td>
<td>0.62</td>
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<tr>
<td>Vascular disease</td>
<td>0.008</td>
<td>2.18</td>
</tr>
<tr>
<td>Body mass index &gt;25 (versus ≤25)</td>
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<td>1.58</td>
</tr>
<tr>
<td>CMV infection</td>
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<td>Monoclonal AB</td>
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<td>Polyclonal AB</td>
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<td>HLA A mm</td>
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<td>HLA B mm</td>
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<tr>
<td>HLA DR mm</td>
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<td></td>
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<td>Shared antigen</td>
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<tr>
<td>Preservation time &gt;20 h (versus ≤20 h)</td>
<td>0.08</td>
<td>1.87</td>
</tr>
<tr>
<td>Donor age &gt;45 (versus ≤45 yr)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Donor cause of death: traumatic (versus nontraumatic)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>ED (versus BD) drainage</td>
<td>0.82</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Multivariate analysis: Risk factors for worse patient survival (eras 3 and 4)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P Value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age &gt;45 (versus ≤45 yr)</td>
<td>0.15</td>
<td>2.39</td>
</tr>
<tr>
<td>Pancreas retransplant</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Kidney retransplant</td>
<td>0.02</td>
<td>7.00</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Body mass index &gt;25 (versus ≤25)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>CMV infection</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Monoclonal AB</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Polyclonal AB</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>HLA A mm</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>HLA B mm</td>
<td>0.048</td>
<td>2.9</td>
</tr>
<tr>
<td>HLA DR mm</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Shared antigen</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Preservation time &gt;20 h (versus ≤20 h)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Donor age &gt;45 (versus ≤45 yr)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Donor cause of death: traumatic (versus nontraumatic)</td>
<td>0.19</td>
<td>0.43</td>
</tr>
<tr>
<td>BD (versus ED) drainage</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

a RR, relative risk; CMV, cytomegalovirus; AB, antibody; mm, mismatch; BD, bladder drainage; ED, enteric drainage.
ney transplant, particularly for recipients whose LD pancreas is from the same donor as their LD kidney and for recipients who accept the slightly higher technical risk as a trade-off for less immunosuppressive therapy posttransplant. However, most of our LD pancreas transplants are now done simultaneously with a kidney in uremic recipients (3).

The overall incidence of CAD pancreas graft loss from technical failures has significantly decreased over time (by more than 50%) from era 2 to era 4. Specifically, the rate of graft thrombosis was only one in 20 in era 4; we attribute this improvement to intravenous administration of heparin for the first 5 d posttransplant and to a 2-d overlap with aspirin, which is continued indefinitely. Improved antibiotic, antiviral, and antifungal prophylaxis (and treatment if necessary) has resulted in no graft losses from infection in era 4.

PAK transplants have become a very safe procedure with TAC-MMF (eras 3 and 4). More than 95% of our recipients were alive at 1 yr and more than 90% at 3 yr. Even recipients subjected to long-term immunosuppression (>5 yr) before a PAK transplant do not have a significant mortality risk, with a survival rate at least as good as for SPK recipients. Recipient age (≤45 versus >45 yr) also did not have a large impact on patient survival rates in eras 3 and 4, nor did vascular disease. Thus, the surgical impact of PAK transplants on patient survival has become minute. Excellent patient survival rates after solitary pancreas transplants have also been reported by other groups (9,11,12).

PAK transplants were more than twice as common at our center after LD (versus CAD) KTA for the entire population across the four eras, simply because most CAD kidney recipients received a pancreas simultaneously from the same donor in all eras but era 1. However, the proportion of cadaver KTA recipients who went on to have a PAK transplant also increased over time; therefore, nearly all kidney recipients who somehow miss getting a pancreas simultaneously will go on to receive one subsequently.

The time interval between the kidney and pancreas transplant has significantly decreased, from an average of more than 3 yr in era 1 to about 1 yr in era 4. In eras 3 and 4, pancreas graft survival has not been different for recipients whose time interval was more than (versus less than) 1 yr.

Kidney graft survival from the time of the PAK transplant has been high throughout all four eras, particularly in eras 3 and 4 (94% at 1 yr). When we compared kidney graft survival in diabetic KTA recipients versus those who subsequently underwent a CAD pancreas transplant, short- and long-term kidney graft survival rates were significantly higher for both LD and CAD recipients in the pancreas group. When we compared kidney graft survival in the PAK group from the time of the pancreas transplant versus kidney graft survival in the diabetic KTA group from the time of the kidney transplant (disregarding the interval between the kidney and pancreas transplant in the pancreas group), the results were still more favorable in the pancreas group, irrespective of the kidney donor source. These results show that kidney survival is not jeopardized by a subsequent pancreas transplant, nor does the mortality rate increase with a subsequent pancreas transplant in already-immunocompromised recipients. Although the results presented are still short-term (only 1-yr data could be presented for era 4 at the time of this writing), graft and patient survival rates in eras 1, 2, and 3 remained higher for PAK (versus KTA) recipients even 5 yr posttransplant. It seems that the subsequent pancreas transplant conveys a clear advantage to the diabetic kidney recipient.

We previously showed that diabetic nephropathy recurs in almost 50% of KTA recipients (13,14). We also showed, in biopsy studies 2 to 10 yr after the pancreas transplant in PAK recipients, a regression of glomerular lesions (15). Moreover, we showed that, for nonuremic PTA recipients, glomerular and tubular basement membrane thickness and the mesangial fractional volume of the glomerulus decreased and basically returned to normal after 10 yr (16). These findings mean that PAK recipients whose diabetic nephropathy recurs in their transplanted kidney will still benefit from a subsequent pancreas transplant—although it might take several years of normoglycemia to reverse the lesions of diabetic graft nephropathy. This advantage would be even more obvious if we did not rely on calcineurin inhibitors for both PAK and KTA recipients, which may cause ongoing deterioration of renal function. Although the levels of calcineurin inhibitors within the first year posttransplant were higher for PAK (versus KTA) recipients, the levels were not different thereafter. Target levels >1 yr posttransplant for CSA in era 2 were 100 to 150 ng/ml for TAC, 5 to 10 ng/ml in eras 3 and 4.

Regarding matching, results were best, in our experience, if the donor and recipient were matched for at least one antigen per HLA locus. The overall number of antigens can be increased by matching the antigens of the previous kidney that were not shared with the recipient. Thus, up to 12 antigens may be available for matching in PAK candidates, increasing the potential for good matching. Although the matching effect in the TAC eras (eras 3 and 4) is not as prominent as in the CSA era (era 2), HLA matching nevertheless has a long-term impact and should not be neglected. Good HLA matching had a greater impact on graft survival in retransplants than in primary transplants.

On the basis of our experience, PAK recipients now enjoy graft and patient survival rates similar to those of SPK recipients. The improvement in PAK results has many causes: better immunosuppression, good matching (preferably one antigen per locus), and close posttransplant monitoring for rejection. Because PAK recipients are already on immunosuppression, the additional risk is mainly that of the surgical procedure; the morbidity rate is now low. In conclusion, PAK transplants should be considered for most diabetic patients who have a functioning LD or CAD kidney graft.

Acknowledgments

The authors thank Mary Knatterud, PhD, for editorial assistance and Heather Nelson for preparation of the article.

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