Transplantation of the Type 1 Diabetic Patient: The Long-Term Benefit of a Functioning Pancreas Allograft

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lthough simultaneous pancreas-kidney transplantation (SPK) is generally believed to be the treatment of choice in type 1 diabetic patients with kidney failure, there is continuing controversy whether SPK is superior to kidney transplantation alone (KTA), especially when a live donor kidney (LDK) is available. This controversy is highlighted by three recent publications authored by Young et al. (1), Weiss et al. (2), and our group (3). Analyzing data from large registries, all three studies compared kidney graft and patient survival in SPK (all from deceased organ donors) and KTA transplants, whereby the KTA grafts were from deceased (DDK) or living donors (LDK). The three studies are summarized in Table 1 (bold) with respect to data source, treatment modality, length of follow-up, and patient and kidney graft survival.

Young et al. and Weiss et al. analyzed U.S. data based on the Organ Procurement and Transplantation Network/United Network for Organ Sharing and the Scientific Registry of Transplant Recipients, respectively. Young and colleagues found superior kidney graft and patient survival in LDK recipients as compared with SPK recipients after a maximum of 7 years of follow-up. No significant difference was found between deceased donor SPK and DDK patients with respect to kidney graft and patient survival.

In contrast, analyzing the international Collaborative Transplant Study (CTS) database, which collects data from 46 countries in five continents, our group found that SPK and LDK yielded clearly superior kidney graft and patient survival as compared with DDK alone. Importantly, in the CTS analysis, patient survival beyond year 10 after transplantation in SPK recipients was significantly better than that of recipients of a LDK without a pancreas graft (hazard ratio = 0.55; $P = 0.005$), as demonstrated for transplants performed between 1984 and 1990 with a follow-up of 18 years. This effect was mainly attributable to a significantly lower rate of cardiovascular death in recipients of a combined pancreas-kidney transplant (SPK 37.0% versus DDK 45.8%, $P = 0.049$; and versus LDK 49.3%, $P = 0.007$). The univariate results were confirmed by multivariate analysis, in which it was taken into account that SPK patients are commonly in a better physical condition at the time of transplantation; that is, with less pre-existing cardiovascular disease than DDK recipients.

Our data are supported by the analysis of Weiss and coworkers who found superior kidney graft and patient survival in type 1 diabetic SPK recipients who had a functioning pancreas allograft 12 months posttransplantation, as compared with SPK patients who had lost their pancreas allograft within the first year after transplantation, but also in comparison to type 1 diabetic LDK and DDK recipients (2). These data support the benefit of a functioning pancreas allograft.

The three studies end up with three different results and therefore lead to different recommendations. Weiss and coworkers actually made no recommendation at all. Young and colleagues made a priority recommendation for LDK in type 1 diabetic patients, whereas our group favored SPK as a first line treatment option for type 1 diabetics. Because the recommendations are so different, critical analysis and comment is warranted.

Crucial Effect of Length of Follow-Up

We believe that the length of follow-up is decisive for valid comparison of different transplant strategies in type 1 diabetic patients. A similar lesson was learned from a comparison of kidney transplant recipients with patients on dialysis. It is known that patient survival after kidney transplantation is inferior to survival on dialysis when the first 244 posttransplant days are considered (4), a finding that most likely relates to risks associated with the transplant procedure itself. However, after approximately 100 days, the mortality risk of transplanted patients equals that of dialysis patients, and beyond day 244 there is an increasing survival benefit for transplanted as compared with waitlisted patients. We note some analogy with respect to kidney transplantation with or without a pancreas. There is a survival benefit in the first years after transplantation (in our study up to year 5 (3)) for LDK as compared with SPK recipients. This can be assumed to be attributable to the larger and more complex surgical procedure as well as the higher rate of postoperative complications associated with SPK (5,6). However, in the long term SPK is superior. It takes time until the
added procedural risk of double-organ transplantation associated with SPK is outweighed by the benefit; namely, improved glycemic control.

The decisive effect of length of follow-up is impressively illustrated in Table 1. Although the studies on transplantation in type 1 diabetic patients listed in Table 1 were based on different populations and different statistical methods, it is apparent that there is an increasing benefit of the combined SPK procedure with length of follow-up. With a mean follow-up of approximately 5 years, studies show in general a survival benefit of SPK over DDK, whereas LDK recipients show the best graft and patient survival. With follow-up from 5 to 10 years several studies show no survival difference between SPK and DDK patients, whereas both procedures are superior to DDK. After even longer follow-up of more than 10 years, which could only be studied in our analysis of the CTS database, superior patient survival is evident in the SPK cohort, even when compared with LDK recipients. The CTS result emphasizes that it takes time until the benefit of glycemic control through SPK becomes evident. It is therefore misleading to judge the efficacy of KTA versus SPK in type 1 diabetics by comparing success rates on the basis of a posttransplant follow-up of less than 5 years.

To further strengthen our point, we reanalyzed the CTS data (Figure 1 and Table 2; for statistical analysis refer to reference 3) and are now able to present for the first time follow-up to year 20 after transplantation for SPK or KTA (the latter from a deceased or living donor). The hazard ratio for patient death 2 to 5 years after transplantation decreased in recent years (Table 1). It becomes obvious that meaningful comparison of the long-term success of SPK with KTA must be performed with substantially longer follow-up than 5 years.

Table 1. Impact of glycemic control on kidney allograft and patient survival (modified from Morath and Zeier [9])

<table>
<thead>
<tr>
<th>Observation Period</th>
<th>Patient Survivala</th>
<th>Kidney Allograft Survival</th>
<th>Source/Databaseb</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to day 244c</td>
<td>Dialysis &gt; DDK</td>
<td>NAd</td>
<td>USRDS</td>
<td>4</td>
</tr>
<tr>
<td>3 to 6 years</td>
<td>SPK = DDK</td>
<td>SPK = DDK</td>
<td>UNOS</td>
<td>10</td>
</tr>
<tr>
<td>0 to 7 years</td>
<td>LDK &gt; SPK = DDK</td>
<td>LDK &gt; SPK = DDK</td>
<td>OPTN/UNOS</td>
<td>1</td>
</tr>
<tr>
<td>Up to 7 years</td>
<td>SPK + P &gt; LDK &gt; DDK</td>
<td>SPK + P &gt; LDK &gt; DDK</td>
<td>SRTR</td>
<td>2</td>
</tr>
<tr>
<td>2 to 9 years</td>
<td>SPK = DDK</td>
<td>SPK = DDK</td>
<td>UNOS</td>
<td>11</td>
</tr>
<tr>
<td>0 to 10 years</td>
<td>SPK &gt; DDK</td>
<td>SPK &gt; DDK</td>
<td>Single center (Ireland)</td>
<td>12</td>
</tr>
<tr>
<td>Up to &gt;10 years</td>
<td>LDK = SPK &gt; DDK</td>
<td>LDK = SPK &gt; DDK</td>
<td>Single center (United States)</td>
<td>13</td>
</tr>
<tr>
<td>4.8 years (mean)</td>
<td>LDK = SPK &gt; DDK</td>
<td>LDK = SPK &gt; DDK</td>
<td>UNOS</td>
<td>14</td>
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<tr>
<td>0 to 12 years</td>
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<td>SPK &gt; DDK</td>
<td>OPTN/UNOS/SRTR</td>
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<tr>
<td>18 years</td>
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<td>SPK = LDK &gt; DDK</td>
<td>CTS</td>
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</tr>
<tr>
<td>20 years</td>
<td>SPK &gt; LDK &gt; DDK</td>
<td>SPK &gt; LDK &gt; DDK</td>
<td>CTS</td>
<td></td>
</tr>
</tbody>
</table>

aP, functioning pancreas allograft at year 1 after transplantation; −P, no functioning pancreas allograft at year 1 after transplantation.
bUSRDS, U.S. Renal Data System; UNOS, United Network for Organ Sharing; OPTN, Organ Procurement and Transplantation Network.
cPatients with different primary diseases of native kidneys.
dNA, not applicable.

Figure 1. Patient survival in type 1 diabetic patients after DDK, LDK, or SPK from deceased donors performed during the period from 1984 to 2007.
2). We interpret this to reflect improvements in postoperative management of SPK patients. Our data suggest that the long-term survival benefit associated with SPK seen for transplants performed between 1984 and 1990 will likely also apply to patients transplanted from 1991 to 2000 and 2001 to 2007. The evolution of the survival curves indicates that the trend for earlier and recent transplants is similar and furthermore suggests that the benefit of glycemic control conferred by a functioning pancreas will become apparent even earlier in recent transplants because of the better initial results of SPK.

As shown by Weiss and colleagues and our own study, success of the combined SPK procedure clearly depends on a functioning pancreas allograft. Fortunately, only 5.4% of SPK patients in the study by Weiss and colleagues who had a functioning kidney graft after 1 year had lost their pancreas graft during the first posttransplant year. Some 95% of SPK patients benefited from the combined procedure, with unadjusted kidney graft and patient survival at 7 years of 72.0% and 88.6%, respectively (as compared with the rates obtained with LDK, which were 63.6% and 80.0%, respectively).

It is a limitation of this comparison that the different studies were based on different patient populations (our study analyzed the international CTS database whereas the two other studies analyzed U.S. transplants). Although participation in the CTS is voluntary, registration of all consecutive transplants performed at a center is mandatory and we have no reason to believe that incomplete reporting of long-term outcome played a role in our analysis (CTS Newsletter 1, 2007; available at http://www.ctstransplant.org; last accessed November 25, 2009). In addition, there might be a difference in the experience of different centers in performing transplants that might bias the comparison of LDK and SPK in favor of SPK. This issue was adequately addressed in our study by comparing only those centers that performed all three different types of transplants (DDK, LDK, and SPK) (3). Another mitigating factor might be that type 1 diabetic patients initially eligible for SPK (inclusion criteria in the study by Weiss and coworkers) may be more healthy than all type 1 diabetic patients (inclusion criteria in the study by Young and coworkers) and that this might affect outcome measures. Detailed information on comorbidity is not available for our study; however, LDK and SPK recipients had the same baseline risks as indicated by the pretransplant evaluation criteria recorded and reported to CTS by the transplant centers (“general evaluation” or “cardiovascular risk”) (3).

### Conclusions

With prolonged follow-up after transplantation there is an increasing survival benefit in terms of kidney graft and patient survival in SPK as compared with KTA recipients. Beyond year 10 after transplantation, SPK is also superior to LDK with respect to patient survival (and even graft survival as shown in our new analysis with 20 years of follow-up). The question remains whether it is justified to place a patient on the waiting list for SPK, with the likelihood that the period of dialysis treatment before transplantation will be lengthened as compared with LDK, for a survival benefit that will be realized at
the earliest 5 to 10 years after transplantation. In this context, Young and coworkers raised an important point; namely, that in light of the current shortage of donor organs the donor pool should be expanded, and they suggested an increased utilization of living donors. We believe that the benefit of early transplantation (an advantage associated with LDK) needs to be balanced against the significant long-term survival benefit associated with SPK. Especially when SPK can be realized after a relatively short waiting time, SPK should be considered as the first choice for most patients (in the Eurotransplant area, where SPK transplants are given priority, the waiting time for SPK is much shorter than for KTA and some SPK recipients are transplanted even before they require dialysis treatment).

What Conclusions Can Be Drawn from the Three Studies?

On the basis of the work of Weiss and colleagues and our own study, a priority recommendation for SPK is warranted. However, as compared with LDK, this conclusion needs to be balanced against a prolonged waiting time with a higher risk of comorbidity and/or death on the waiting list for SPK because of a shortage of donor organs. The patient should receive appropriate information on all available procedures with their potential risks and benefits, and caregivers together with the patients should decide every single case individually on the most appropriate transplantation strategy.

Disclosures

None.

References