Editorial

Should We Be Performing Pancreas Transplants?

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The vast majority of the 1 million people with Type I diabetes in the United States are treated with maintenance exogenous insulin therapy. Only about 1 in 1000 (approximately 1300/year) are treated with transplantation. The whole organ pancreas transplant has been one of the most difficult organs to transplant successfully because of a high risk for pancreatitis, graft thrombosis and rejection. A decade ago, one could question the wisdom of performing a pancreas transplant in any patient. However, with improvements in immunosuppression and patient management, the field has improved steadily. Simultaneous pancreas kidney (SPK) transplantation was the first to show an improvement and now several reports have suggested that SPK leads to increased patient survival and a better quality of life compared to a kidney transplant alone. In solitary pancreas transplantation, either pancreas after kidney (PAK) or pancreas transplant alone (PTA), a survival benefit has been more difficult to ascertain. In fact, Venstrom et al. actually reported a survival disadvantage for PAK in their paper published in the Journal of the American Medical Association (1). In the present issue of AJT, Gruessner et al. revisit the question of the survival benefit of PAK, with their data indicating, that with the current cohort of patients and current follow-up, neither a survival advantage nor disadvantage could be found.

The survival benefits of transplantation are most often assessed retrospectively, as prospective studies are often not feasible because of ethical concerns (e.g. if a procedure is perceived to be vastly superior), but also because of financial, patient resource and statistical power constraints. Even the most sophisticated retrospective comparisons are plagued by important selection biases that often times are not readily recognizable by the clean numbers presented in analysis tables. An obvious bias in assessing a survival advantage of transplantation lies in the fact that the selection process is geared to direct organs toward those patients who are healthy enough to safely undergo transplantation, which leaves sicker patients in the non-transplanted group. A partial but far from perfect solution to this bias is to use as the comparison group, patients that have been cleared for and are awaiting transplantation. It is unclear though, how to most appropriately handle this comparison group. For example, the decision of whether or not to censor patients who go off the waiting list does not make the reference group more or less appropriate, but it clearly changes the mortality risk of the comparison group and perhaps the result of the analysis. There is really no ideal way of handling all the potential biases, and both the Venstrom and Gruessner paper have their own underlying biases in how they handle the reference group.

Using patients awaiting kidney transplantation as the reference group, Wolfe et al. (2) have delivered quite credible evidence that kidney transplantation confers a survival benefit over maintenance dialysis. The reason this data has received such widespread acceptance is that it is very reproducible in different populations, like high-risk patients, and patients in different countries, and because the magnitude of the effect is quite impressive and long lasting.

It is quite typical for the mortality risk profile of transplantation to be burdened by an increased initial risk for death, because of the peri-operative mortality and possible effects of initially more potent immunosuppression. In fact this is the case not only in kidney, but also in pancreas transplantation, as documented by both Gruessner in the present issue of AJT, as well as the Venstrom paper. The higher the initial mortality risk, the longer it takes to show the potential long-term benefits. This is one of the reasons why the Venstrom paper showed a significant overall risk for PAK with shorter follow-up, while the Gruessner paper with longer follow-up showed a re-equilibration with the risk being neutral, meaning that the initial peri-operative risk had been made up for by long-term benefits during the time of follow-up. Whether this favorable trend would continue with even more extensive follow-up, translating ultimately into a survival advantage of PAK, remains to be seen. A second point that can confound this type of analysis and is nicely documented by the Gruessner paper is that changing patient selection patterns can change risks over time. In fact in the analysis limited to 2000 the first 90-day mortality risk was more than four-fold; while in the analysis including more recent transplants the same early mortality risk was down to around twofold,
indicating possibly a better preoperative screening of patients, but possibly also improvements in the procedure and post-operative care. For that reason, the analysis including the more recent cohort had to make up for less upfront risk and had also for this reason a better chance to show a risk equilibration over time.

Based on the currently available data it does not seem to be possible to extrapolate a cumulative survival advantage of a PAK, but clearly there is an early toll based on perioperative mortality that is probably made up with longer follow-up, and if the observed trends were to hold true could eventually even translate even into a mortality benefit of this procedure considering sufficient follow-up. The early mortality calls the attention on the patient selection process and suggests that the overall benefit of the procedure could be importantly influenced by adequate patient selection and this has probably already started to happen in the more recent years.

The central question is: should we be performing pancreas transplants? In answering this question, patient mortality is an important but not the sole consideration. Quality of life and impact on secondary complications also should be assessed. Considering all of these outcomes, it appears that for SPK patients the answer is yes. For PAK and PTA, based on current data, the answer is that there may not be a demonstrable survival benefit with transplant and other factors such as the individual patient’s risk and the expertise of the transplant program might be additional considerations. The results of pancreas transplantation, especially PAK and PTA, have improved in recent years and both procedures have become much more common. We believe that it is important to periodically assess not only the overall outcomes as these studies have done, but also to emphasize the need for more carefully controlled studies that might identify patients who achieve the greatest benefit from the pancreas transplant.

References