

Type 2 Diabetes: The Best Transplant Option Is Still Uncertain

David J. Cohen* and Lloyd E. Ratner[†]

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The transplant menu is vast for those with ESRD and diabetes mellitus. The transplant community has struggled for a long time to identify the best treatment and the most equitable allocation of scarce kidneys and pancreata. These transplant options include deceased donor kidney transplant alone (DDKA), live donor kidney transplant alone (LDKA), simultaneous pancreas-kidney transplant (SPK), or DDKA/LDKA followed by pancreas after kidney transplant (PAK). It is unclear which patients will be best served by each of these options. Geographic disparities in waiting times and access to transplantation add another level of complexity to this problem, as does the dichotomy between type I (T1DM) and type II diabetic (T2DM) patients (which has largely dictated who gets a pancreas transplant) and the heterogeneous pathophysiology of T2DM.

Despite a national “epidemic” of diabetes, and an active kidney transplant waiting list with roughly 15,000 patients with diabetes, pancreas transplantation remains underused. Tremendous geographic disparities exist in the rate of pancreas transplantation, indicating that practice patterns influence utilization more than need. In fact, many centers do not offer them to their patients who might benefit. The overall number of pancreas transplants performed has consistently decreased over the last 7 years. The number of pancreas transplants performed in the United States peaked at 1484 in 2004 and has steadily declined since (Figure 1). Only 1177 pancreas transplants were performed in 2010 (<http://optn.transplant.hrsa.gov>), and the number of SPK transplants performed across the United States varies widely between donor service areas, unrelated to the size of the population (Figure 2). Also, pancreas allocation policy that determined whether patients were pushed toward SPK versus PAK differ considerably based on local preferences and allocation variances.

In this context, United Network for Organ Sharing (UNOS) elected to address the issue of pancreas allocation. The new policy would have all kidneys and pancreata from donors deemed to be appropriate offered first to SPK recipients (*i.e.*, allocation of the kidney would follow allocation of the pancreas). However, because of their numbers, the potential exists for T2DM patients to overwhelm the system and use all the younger better kidneys (if allocated with pancreata), thus placing nondiabetic patients at a disadvantage. In response to this concern, UNOS issued regulations to define eligibility

criteria loosely based on the physiology of diabetes mellitus. In essence, these regulations impose limits on the number of patients with diabetes that receive pancreas transplants: they can only make up no more than 15% of the national list, must require insulin, and either have a C-peptide ≤ 2 ng/ml (essentially, T1DM patients) or a C-peptide > 2 ng/ml and a body mass index < 30 kg/m² (likely to include substantial numbers of T2DM patients). UNOS sought to eliminate regional disparities in allocation by changing national policy. These policies are also designed to encourage pancreas utilization, while more or less reflecting current practice, and to maintain the availability of better-quality kidneys for kidney alone candidates if SPK listing increases dramatically.

Although, at present, with little to no regulation as to recipient selection in terms of T1DM or T2DM for SPK (or PAK), there has hardly been great enthusiasm for pancreas transplantation in T2DM. This is reflected in the relative numbers of T1DM versus T2DM who have received pancreas transplants (Table 1). Pancreas transplantation has generally been considered suitable only for T1DM patients (classically thin, ketosis prone, unable to produce insulin because of autoimmune β -cell destruction, C-peptide levels extremely low or undetectable). There is continued uncertainty as to whether T2DM patients (classically obese, insulin resistant, with normal to elevated C-peptide levels) are appropriate pancreas transplant candidates.

However, concepts have evolved considerably: it is increasingly clear that the pathophysiology of T2DM is heterogeneous and that many T2DM patients are likely to become euglycemic after pancreas transplantation.

What has the most recent experience with pancreas transplantation in T2DM, limited as it may be, taught us thus far? Gruessner and Sutherland (1) summarized the UNOS and International Pancreas Transplant Registry data from 2000 to 2004 and reported no difference in outcomes (patient or pancreas graft survival) in those with T2DM versus T1DM. Orlando *et al.* (2) reviewed several single center reports and also found equivalent outcomes after SPK, regardless of whether the patients were classified as having T1DM or T2DM. Sampaio *et al.* (3) reviewed the UNOS database and analyzed outcomes in all primary adult SPK recipients between 2000 and 2007. Of the 6756 recipients, 91.4% were classified as T1DM. They found that, after risk adjustment,

*Department of Medicine, Kidney and Pancreas Transplantation, and [†]Department of Surgery, Kidney and Pancreas Transplantation, Columbia University Medical Center, New York, New York

Correspondence: Dr. David J. Cohen, Department of Medicine, Nephrology Division, Columbia University Medical Center, 622 West 168 Street, Room PH 4-124, New York, NY 10032. Email: djc5@columbia.edu

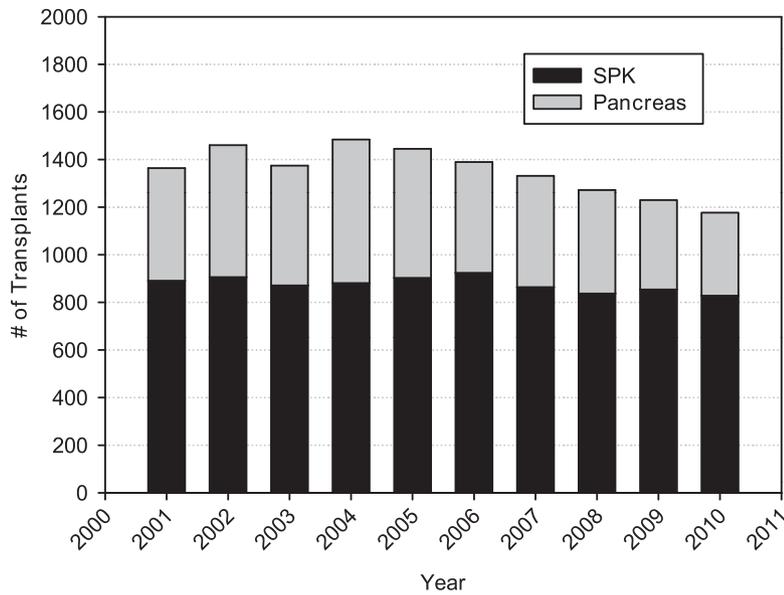


Figure 1. | Pancreas transplantation in the United States has declined overall since 2004. Simultaneous pancreas-kidney transplant remains the dominant form of pancreas transplantation.

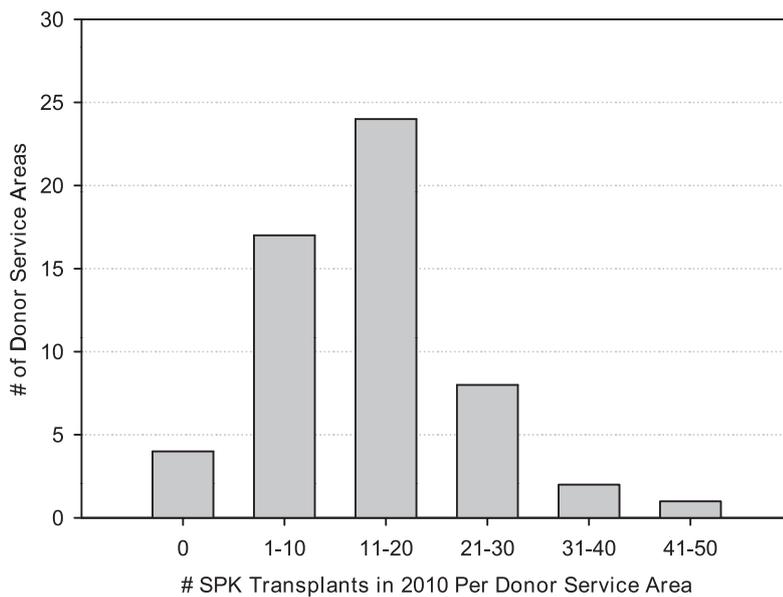


Figure 2. | Pancreas transplantation is performed at transplant centers within 56 of the 58 federally designated donor service areas (DSAs). There are ≤20 simultaneous pancreas-kidney transplant transplants performed annually for type 1 and type 2 diabetic patients combined in the vast majority of those 56 DSAs.

outcomes (death, kidney allograft failure, and pancreas allograft failure) were no different for T1DM versus T2DM patients at 5 years. Selection criteria were not available, and it can be safely assumed that they varied somewhat, but most were probably “T1DM-like” (nonobese, low C-peptide, low insulin requirements).

SPK is not the only type of pancreas transplant available for patients with diabetes, T1DM or T2DM. A review of pancreas transplant outcomes in the United States by Gruessner *et al.* (4) indicated that overall results for PAK remain inferior to those obtained with SPK, almost entirely

because of immunologically related pancreas graft failure. However, they did not distinguish outcomes for T1DM versus T2DM patients. In this issue of *CJASN*, Wiseman and Gralla (5) do not address this issue, but do address the important issue of which transplant is best for the vast majority of patients with diabetes with advanced renal insufficiency (those with T2DM): SPK or kidney transplant alone? Under the new UNOS regulations, these patients, if listed, will now be prioritized for SPK transplants.

The authors reviewed the UNOS database and compared outcomes of several transplant options for T2DM patients:

Table 1. Type of diabetes and access to transplantation in the United States

	Type 1	Type 2
Percent of all patients with diabetes in United States	5%–10%	90%–95%
Percent of all diabetic patients on active kidney transplant list	15.2% ^a	84.8% ^a
Percent of all diabetic patients on active SPK list	89.3% ^a	10.3% ^a
Percent all diabetic patients on active PAK list	94.5% ^a	5.5% ^a
Percent of SPK recipients	92.6% ^b	7.4% ^c
Percent of PAK recipients	95.9% ^b	4.1% ^c

SPK, simultaneous pancreas-kidney transplant; PAK, pancreas after kidney transplant.
^aBased on Organ Procurement and Transplantation Network data as of February 17, 2012 (7).
^bPercent of transplants in patients with insulin-dependent diabetes mellitus from 2000 to 2008.
^cPercent of transplants in patients with non-insulin-dependent diabetes mellitus from 2000 to 2008.

DDKA, LDKA, or SPK. Patients were selected from the database to conform to one of the new UNOS criteria—body mass index <30 kg/m². Patients were further excluded from their analysis based on an age limitation of <18 or >59 years old, in an attempt to reflect current practice, although this is not one of the UNOS SPK allocation criteria. As Wiseman and Gralla note, over a 9-year period, there have only been 424 SPKs in this subgroup of T2DM. Overall, in these T2DM patients, approximately 62% received DDKA, 31% received LDKA, and only 7% received SPK. Their data demonstrated that kidney quality remains a dominant influence on outcome—T2DM recipients of LDKA transplants have better long-term patient and kidney graft survival (both unadjusted and death-censored) compared with SPK recipients, although this is in the absence of any adjustment for factors such as donor age, recipient waiting, or ESRD duration. On the other hand, overall SPK recipients fared better than DDKA recipients. However, when these latter outcomes were adjusted for donor and recipient risk factors known to influence patient and graft survival, the added benefit of a pancreas for comparable patients receiving comparable kidneys was markedly attenuated and was no longer statistically significant, although there remained a trend in favor of SPK, which might well become significant after further follow-up. This is particularly true in light of previous work by Weiss *et al.* (6) that demonstrates that a functional pancreas allograft significantly improves patient and kidney graft survival. This paper unfortunately does not factor pancreas allograft outcomes into their analysis, and although it casts some doubt on the value of SPK in T2DM, the question is not fully answered.

As the authors themselves note, in addition to patient and kidney graft survival, the influence of the pancreas allograft on quality of life and diabetic complications is also extremely important and would certainly be of value in

counseling patients in their choice of treatment, but these data were not available for this analysis. Other limitations, common to most database analyses, are the unknown selection criteria used in steering patients toward DDKA or LDKA versus SPK, including C-peptide levels. We continue to lack data on the outcome of PAK transplantation in T2DM patients. If a suitable live donor is available, should a T2DM patient get LDKA followed by PAK?

It is surprising that UNOS has adopted a policy that potentially restricts access to SPK transplantation for T2DM patients when so little data exist as to which patients will most benefit from this option and overall pancreas transplantation is underused. Fear that preferential SPK allocation to T2DM recipients will reduce kidney availability for nonpatients with diabetes is unfounded. Only 424 SPK transplants were performed in T2DM patients over a 9-year period, which is an average of only 0.8 SPKs transplants per year for each of the 58 federally designated donor service areas. This is hardly a worrisome number. Thus, we believe that the new policy may be misguided.

Regardless of the new UNOS allocation policy, it is highly unlikely that there will to be a surge of SPK transplants in T2DM patients. Whatever the impact of this policy, careful and thorough pretransplant data collection and detailed follow-up of those T2DM patients who do receive SPK transplants are warranted to assess the impact of new allocation rules on diabetic and nondiabetic ESRD patients and to help guide future treatment decisions for the majority of diabetic ESRD patients. Wiseman and Gralla have importantly contributed to this conversation.

Disclosures

None.

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See related article, “Simultaneous Pancreas Kidney Transplant versus Other Kidney Transplant Options in Patients with Type 2 Diabetes,” on pages 656–664.