

Preemptive Transplantation for Patients With Diabetes-Related Kidney Disease

Bryan N. Becker, MD; Sarah H. Rush, MSW; Dawn M. Dykstra, BA; Yolanda T. Becker, MD; Friedrich K. Port, MD, MS

Background: Preemptive kidney transplantation (PreKT) before initiation of chronic dialysis has been examined recently with favorable results as the most effective treatment for kidney failure. Given that few of these studies are disease specific, the present analyses investigated the outcomes of PreKT by transplantation option and diabetes type.

Methods: The impact of PreKT on posttransplantation mortality and graft failure was examined in 23 238 adults with type 1 and type 2 diabetes mellitus (DM), receiving either living or deceased donor kidneys or undergoing simultaneous pancreas-kidney (SPK) transplantation between January 1, 1997, and December 31, 2002.

Results: The PreKTs were provided to 14.4% of patients with type 1 DM and 6.7% of patients with type 2 DM. Cox regression models were used to estimate the effect of PreKT on the adjusted risk ratio (RR) of graft failure and mortality. After adjusting for multiple fac-

tors, PreKT in this era was associated with lower RR of mortality only among type 1 and type 2 diabetic recipients of transplants from living donors and SPK transplant recipients with type 1 DM (RR, 0.50-0.65; $P < .007$ for each). The effect on graft failure was less pronounced, significant only for preemptive SPK transplant recipients (RR, 0.79; $P = .01$ vs nonpreemptive SPK transplant recipients).

Conclusions: These analyses suggest that PreKT has significant benefits for subsets of patients with types 1 and 2 DM and end-stage renal disease. It also suggests a time trend toward less benefit from preemptive transplants from deceased donors in more recent years compared with the early 1990s. This observation and the discrepancies between RR of graft loss and RR of mortality deserve further study.

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DIABETES MELLITUS (DM) continues to increase more rapidly as a cause of end-stage renal disease (ESRD) than any other cause throughout the world.^{1,2} Perhaps most striking is that DM has become the major cause of ESRD in industrialized countries.³ It is apparent that this trend likely will continue, in part because of improvements in mortality rates for hypertension and cardiovascular diseases.^{4,6} This improvement in survival allows more of these individuals to reach advanced kidney failure (stage 5 chronic kidney disease). Treatment options for this condition include dialysis and transplantation. However, lifespan after initiating dialysis with DM-related ESRD remains shorter than that demonstrated for other causes of ESRD.⁷ Many individuals with DM elect transplantation as treatment for their ESRD because this subgroup of patients has been shown to benefit from transplantation relative to continuing dialysis.⁸

Transplantation options differ depending on type of DM for patients at or near ESRD. For patients with type 1 and type 2 DM, these options include kidney transplants from deceased and living donors; patients with type

1 DM have the additional options of deceased donor simultaneous pancreas-kidney (SPK) and islet transplantation. Simultaneous pancreas-kidney transplantation has been attempted in some individuals with type 2 DM.^{9,10} However, this approach has not met with uniform success and hence is not a primary consideration for diabetic individuals with end-stage organ disease who do not have type 1 DM. One additional option for individuals with type 1 DM and kidney failure is pancreas transplantation after kidney transplantation. This option has received great scrutiny over the last 2 years with a mixed assessment of its survival benefit.^{11,12}

Given the strong relationship between kidney failure and survival in individuals with DM, we chose to examine transplantation as a treatment option for kidney failure and, in particular, its timing in relation to the possible success of the procedure. Preemptive kidney transplantation (PreKT) (transplantation prior to initiating dialysis) vs transplantation after a period of dialysis has been examined recently in a set of studies that analyzed the US Renal Data System (USRDS) and Organ Procurement and Transplantation Network (OPTN) data sets.^{13,14} In these studies, individuals who received

Author Affiliations: Departments of Medicine (Dr B. N. Becker) and Surgery (Dr Y. T. Becker), University of Wisconsin–Madison; and Scientific Registry of Transplant Recipients/University Renal Research and Education Association, Ann Arbor, Mich (Mss Rush and Dykstra and Dr Port).

PreKT had improved allograft survival and a reduced risk for death; however, there was a lack of in-depth focus on disease subsets. Disease-specific data are necessary to counsel patients regarding the risks and benefits of a therapy. For ESRD, the prototypical underlying condition is DM. Yet, DM represents an amalgamation of disease types and transplant options. While Meier-Kriesche and Kaplan¹³ noted a beneficial effect for PreKT in diabetes-related kidney disease, their analysis did not subdivide individuals by diabetes type nor did it include individuals who had received an SPK transplant. The present study examined the impact of PreKT in individuals with kidney failure due to either type 1 or type 2 DM. We hypothesized that PreKT in this group of individuals would be associated with improved survival regardless of transplant option or diabetes type.

METHODS

SOURCE OF DATA AND STUDY POPULATION

Data were obtained from the Scientific Registry of Transplant Recipients. This registry includes data collected by the OPTN, with linkages to data from the Centers for Medicare and Medicaid Services (CMS) for patients with ESRD and to the Social Security Death Master File (SSDMF). The study was approved by the Health Resources and Services Administration (HRSA), which has determined that it satisfies the criteria for the institutional review board exemption described in the "Public Benefit and Service Program" Provisions of 45 CFR 46.101(b)(5) and HRSA Circular (03).

All diabetic (type 1 and type 2) recipients of a kidney transplant from a first living or deceased donor between January 1, 1997, and December 31, 2002, were considered for analysis, with the exception of pediatric recipients younger than 18 years ($n=26$). Recipients were followed through June 30, 2003. Transplants from deceased donors were modeled as 2 types: kidney transplantation alone or SPK. Patients with missing data on follow-up time were excluded ($<1\%$). Overall, 23 238 recipients with DM were available for study ($>99\%$). Kidney graft failure was defined as a record of graft failure, death, or retransplantation. Patient death was determined by a death record in any of the data sources, including CMS and the SSDMF, whereas graft failure was ascertained using only OPTN data.

DEFINITIONS

Diabetes mellitus was determined by the transplantation diagnosis recorded on the OPTN Kidney Transplant Recipient Registration Form or an indication of DM on the OPTN Kidney Transplant Candidate Registration Form. Priority was given to the transplantation diagnosis on the recipient form; this information was supplemented by DM status from the candidate form for any missing and nondiabetic diagnoses. Simultaneous pancreas-kidney transplant recipients were all coded as having type 1 DM as (1) the intent of the transplantation center would have been to list these individuals as type 1 DM, given the standard practice of SPK transplantation,¹⁵ and (2) because the number of SPK transplant recipients who possibly had type 2 DM was exceedingly small ($<2\%$ total). *Preemptive kidney transplantations* were defined as transplantation among recipients with less than 1 week of dialysis prior to surgery. The *date of first dialysis* was determined using CMS data files. Scientific Registry of Transplant Recipients data were used to supplement missing CMS data. *Insurance status* was coded using primary and secondary sources of payment and categorized as (1) government (Medicare and

Table 1. Adult Kidney Transplant Recipients by Preemptive Status, 1997-2002

Transplant Type	PreKT, No.	Non-PreKT, No.
Type 1 DM		
Living donor KTA	714	2438
Deceased donor KTA	169	3375
Deceased donor SPK	824	4305
Type 2 DM		
Living donor KTA	554	3173
Deceased donor KTA	215	7471

Abbreviation: DM, diabetes mellitus; KTA, kidney transplantation alone; preKT, preemptive transplantation; SPK, simultaneous pancreas-kidney.

Medicaid); (2) personal (Medicare [primary] and other source of payment, private only, health maintenance organization only, or private/health maintenance organization [primary] and other source of payment); and (3) other (other source of payment or missing source of payment). Simultaneous pancreas-kidney transplant recipients had the source of payment for the kidney combined with that of the pancreas by giving priority to personal insurance, then government, and finally other sources of payment.

STATISTICAL ANALYSIS

Compared with transplantation after chronic dialysis, the effect of PreKT on graft failure was modeled as the time from transplantation to kidney graft failure (including indication of return to dialysis), death, or retransplantation, using Cox proportional hazards regression. Patients were censored at the earliest of the following: last known follow-up date, the maximum date for which follow-up information was expected, or the end of study (June 30, 2003). The relative risk of death was modeled as the time from transplantation to death, using Cox regression, censored at the earliest of either the maximum date for which follow-up information was expected or June 30, 2003. These Cox models were developed to determine the adjusted and unadjusted relative risk of graft failure and death by type 1 or type 2 DM and transplant option (living donor, deceased donor, or SPK). Kidney graft failure and patient mortality models were adjusted for the following recipient variables: age, sex, race, ethnicity, panel reactive antibody (PRA) at time of transplantation, blood type, educational level, employment status at time of transplantation, and source of payment. The models also were adjusted for donor age, sex, race, and ethnicity. Transplantation-specific variables in the model included degree of HLA mismatch, year of transplantation, and whether the transplantation was preemptive. Models also included interactions by donor source and DM type to estimate subgroup differences in survival.

All analyses were carried out using the statistical software package SAS version 8.2 (SAS Institute, Cary, NC). $P<.05$ was considered significant.

RESULTS

The study population consisted of 23 238 diabetic individuals 18 years or older who underwent a first kidney transplantation alone or SPK transplantation in the United States between January 1, 1997, and December 31, 2002 (**Table 1**). There were 11 825 (50.9%) recipients with type 1 DM and 11 413 (49.1%) individuals with type 2 DM. This is a different distribution of type 1 and type 2 DM than that apparent in the general population, where most individuals have type 2 DM. Nearly half ($n=11\ 230$;

Table 2. Characteristics of Adult Kidney Transplant Recipients With DM, 1997-2002

Characteristic	% or Mean
Preemptive transplantation	10.7
Transplant type	
Deceased donor kidney	48.3
Deceased donor SPK	22.1
Living	29.6
Type of diabetes	
Type I	50.9
Type II	49.1
Source of payment	
Personal	84.5
Government	12.3
Other/missing	3.2
Recipient age, y	
18-34	12.9
35-54	51.9
≥55	35.3
Recipient race	
Asian	2.6
African American	20.8
White	74.2
Other	2.4
Recipient ethnicity Hispanic	12.0
Male	61.4
Recipient blood type	
A	40.0
B	11.8
AB	4.8
O	43.5
Panel reactive antibody	
≤9	73.2
10-40	3.8
41-79	1.6
≥80	1.2
Missing	20.2
Education	
Less than high school	5.1
High school	35.5
College/postgraduate	35.4
Missing	23.9
Employment status at transplantation	
Employed	28.8
Disease affects employment	38.2
Other	18.6
Unknown	14.4
HLA mismatch	
0	11.8
1	4.2
2	11.5
3	21.5
4	20.1
5	19.7
6	10.4
Donor age, y	
≤17	11.8
18-34	33.8
35-54	41.0
≥55	13.1
Donor race	
Asian	1.9
African American	12.0
White	84.9
Other	1.1
Donor ethnicity Hispanic	11.0
Donor male	54.1
Donor blood type	
A	35.9
B	9.8
AB	2.6
O	51.7

Abbreviations: DM, diabetes mellitus; HLA, human leukocyte antigen; SPK, simultaneous pancreas-kidney.

48.3%) received kidney transplants from deceased donors, while 6879 (29.6%) received kidney transplants from living donors and 5129 (22.1%) underwent SPK transplantation. Over 2000 individuals (n=2476; 10.7%) underwent PreKT. This represents 14.4% of type 1 DM recipients (n=1707) and 6.7% of type 2 DM recipients (n=769). The patient characteristics for the entire group of transplant recipients with DM are given in **Table 2**.

GRAFT FAILURE

Preemptive SPK transplantation was associated with a lower risk for graft loss (**Table 3**; adjusted risk ratio [RR] graft failure, 0.79; $P = .01$) compared with SPK with prior dialysis. Preemptive transplantation conferred no statistically significant effect on graft failure among individuals with type 2 DM who received a kidney transplant. However, there was a suggested lower risk for type 2 diabetic recipients of kidney transplants from living donors (RR, 0.81; $P = .09$). There also was a significantly lower adjusted risk of graft failure for transplants from living vs deceased donors (preemptive and nonpreemptive) for recipients with either type 1 (RR, 0.571; $P < .001$) or type 2 DM (RR, 0.649; $P < .001$; data not shown).

PATIENT MORTALITY

Transplants from living donors were associated in this analysis with a lower adjusted mortality risk for both type 1 and type 2 DM recipients (RR for transplants from living vs deceased donors, 0.628 [$P < .001$] for type 1 and 0.685 [$P < .001$] for type 2). Results in Table 3 show that for patients with type 1 DM, PreKT with transplants from living donors and SPK transplantation conferred a significantly lower adjusted mortality risk (RR, 0.57 [$P = .002$], and RR, 0.50 [$P < .001$], respectively). The survival benefit for PreKT with transplants from living donors was also evident for recipients with type 2 DM (RR, 0.65; $P = .007$).

COMPARATIVE ANALYSES

Because these results differed somewhat from recently published work by Meier-Kriesche and Kaplan,¹³ we performed comparative analyses examining an earlier cohort of diabetic patients (1988-1997) included in their study. First, we analyzed patient mortality and graft failure (with and without death censored) in this earlier cohort using our model, which adjusted for nearly all the factors they described. Adjusted patient mortality and graft failure rates were similar to their report (data not shown). We then assessed our more recent cohort of all diabetic transplant recipients (January 1, 1997, to December 31, 2002) in aggregate and compared it without adjustment to the prior period (**Table 4**). Combining DM types 1 and 2, PreKT conferred a significant benefit in terms of lower RR of graft failure for recipients of transplants from living donors and SPK transplants between 1997 and 2002 (unadjusted RR for transplants from a living donor, 0.77 [$P < .001$]; unadjusted RR for SPK transplants, 0.78 [$P = .01$]). While this finding appears consistent with the earlier period, recipients of transplants from deceased donors no longer showed a significant graft survival benefit from PreKT in the later cohort (unadjusted RR, 0.89; $P = .28$). Similarly, for RR of

mortality, PreKT was associated with reduced RR for recipients of transplants from living donors and SPK transplants (unadjusted RR, 0.58 [$P < .001$], and unadjusted RR, 0.48 [$P < .001$], respectively), whereas transplants from deceased donors in the later group appeared to have less benefit (unadjusted RR, 0.79; $P = .08$).

COMMENT

Diabetes mellitus is the single most prevalent cause of kidney failure in the United States.¹⁶ Therefore, treatment options have important implications for the community with ESRD. Recent publications generally have supported the choice of PreKT for individuals with kidney failure. Yet, our study, by focusing on DM type and transplant option, suggests that PreKT conveys a survival advantage only for those recipients with DM (both types) who receive transplants from living donors, or, in the case of recipients with type 1 DM, SPK transplants. The lack of congruence between patient mortality and graft failure in our analyses suggests that factors other than the kidney transplant itself likely influence this survival advantage.

Why the disagreement among studies? Changes in posttransplantation care have altered outcomes in the last decade. In particular, use of mycophenolate mofetil has decreased rates of acute rejection¹⁷ and chronic graft loss.¹⁸ The cohort evaluated in this study was more likely to receive mycophenolate mofetil than the earlier cohort, based on when this drug moved into practice, as shown by the Scientific Registry of Transplant Recipients.¹⁹ Kidney quality and early outcomes also may be factors. It is interesting that 1-year graft survival for type 1 DM recipients of transplants from deceased donors who underwent PreKT in the 1988-1997 cohort was 87.5% vs 84.1% for the non-PreKT group. In the 1997-2002 cohort, 1-year graft survival for type 1 DM recipients of transplants from deceased donors who underwent PreKT fell to 86.7%, while 1-year graft survival for non-PreKT recipients increased to 88%. Also noteworthy is the increase in the number of transplantations in recipients with type 2 DM, from 4083 in the 1990-1997 cohort to 11 413 in the 1997-2003 group. The increasing number of patients with type 2 DM reflects changes in the ESRD population,⁷ and the likelihood that the comorbid conditions of such patients at onset of ESRD may be more severe. We suspect the more recent cohort had greater risk of complication and death attributable to underlying illness and that this affected results on time trends (Table 4).

Observational analyses like those in this study can show

association between PreKT and outcomes. This is useful for generating hypotheses. We acknowledge that database analyses in transplantation have limitations, including potential hidden bias, lack of controlled data, and the inherent nature of applying retrospective approaches to the examination of large data sets.²⁰ As such, they cannot directly inform the mechanisms or modes of action; conclusions drawn from them cannot confirm causation.

Several implications can be suggested from this study. First, such data could help in counseling diabetic patients regarding advantages of PreKT, at least for some groups, because the benefits of PreKT have not been documented previously by diabetes type. One could adopt patient-specific strategies similar to that suggested by Ishani et al²¹ regarding timing of transplantation (the glomerular filtration rate reaches levels between 15 and 10 mL/min). In addition, this study provides a good foundation for advocating preKT with transplants from living donors for survival benefit.

For individuals with type 1 DM, SPK transplantation may provide a better opportunity to lead a longer life with a functioning allograft. Our results suggest a significant benefit of preemptive SPK with respect to mortality and graft failure for these patients. Presently, transplant centers may be able to obtain kidneys for SPK transplants via an algorithm developed by OPTN. In some instances, this could lengthen waiting times for all other individuals (DM and non-DM) who hope to receive kidney transplants. As organ allocation policies are reviewed and refined over time, there may be changes in kidney allocation that affect distribution of SPK transplants. Such schema will have to take into consideration the evident success of SPK transplantation.

Table 3. Adjusted Risk Ratio (RR) of Mortality and Graft Failure for PreKT vs Non-PreKT Among Recipients With Diabetes Mellitus (DM), 1997-2002

Recipient Characteristic	RR (P Value), PreKT vs Non-PreKT	
	Mortality	Graft Failure
Type 1		
Living donor KTA	0.57 (.002)	0.85 (.23)
Deceased donor KTA	0.88 (.53)	0.99 (.96)
Deceased donor SPK	0.50 (<.001)	0.79 (.01)
Type 2		
Living donor KTA	0.65 (.007)	0.81 (.09)
Deceased donor KTA	0.92 (.63)	1.04 (.80)

Abbreviations: KTA, kidney transplantation alone; PreKT, preemptive kidney transplantation; SPK, simultaneous pancreas-kidney.

Table 4. Unadjusted Risk Ratio (RR) of Mortality and Graft Failure for PreKT vs Non-PreKT Among Recipients With DM: Cohort Comparison, 1988-1997 vs 1997-2002

Transplant Type	RR Mortality (P Value)		RR Graft Failure (P Value)	
	Oct 1988–Jun 1997	Jan 1997–Dec 2002	Oct 1988–Jun 1997	Jan 1997–Dec 2002
Living donor KTA	0.62 (<.001)	0.58 (<.001)	0.72 (<.001)	0.77 (<.001)
Deceased donor KTA	0.64 (<.001)	0.79 (.08)	0.74 (<.001)	0.89 (.28)
Deceased donor SPK	0.78 (.004)	0.48 (<.001)	0.89 (.07)	0.78 (.01)

Abbreviations: DM, diabetes mellitus; KTA, kidney transplantation alone; PreKT, preemptive kidney transplantation; SPK, simultaneous pancreas-kidney.

The benefit of deceased donor kidney transplantation vs remaining on dialysis has been clearly documented for diabetic transplant candidates by Wolfe et al⁸; the even greater benefit with kidney transplants from living donors has been documented as well.²² Future analyses need to test the benefit of preKT with transplants from deceased donors compared with outcomes for patients placed on the waiting list prior to dialysis. This might represent a unique opportunity to calculate survival analyses using a level of glomerular filtration rate as a starting point rather than an intervention. Unfortunately, such data are not widely available at the moment, and the data from Ishani et al²¹ did not encompass the important subset of patients who have significant reductions in glomerular filtration rate but are not yet receiving dialysis. Such individuals totaled 9.3% of candidates (n=3166; total=33 395) with diabetes placed on the kidney waiting list between 2000 and 2003. This was comparable to the 10.1% rate of preemptive listing in the nondiabetic population. Finally, it is possible that the observed differences between outcomes for patients with type 1 vs type 2 DM may actually be larger because some patients with type 2 DM may be misclassified as type 1.²³⁻²⁶ This further could influence the timing and choice of transplantation, especially with the ever-increasing proportion of ESRD cases attributable to patients with type 2 DM.

This analysis demonstrates that PreKT confers a survival benefit in subsets of transplant recipients with type 1 and type 2 DM. It also suggests a time trend toward reduced benefit from PreKT with transplants from deceased donors from the early 1990s to the 1997-2002 era. This latter observation and the discrepancies between RR graft failure and RR mortality deserve further study.

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Correspondence: Friedrich K. Port, MD, MS, University Renal Research and Education Association, 315 W Huron, Suite 260, Ann Arbor, MI 48103 (fport@urra.org).

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