The Change in Allograft Function among Long-Term Kidney Transplant Recipients

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Abstract. Long-term kidney allograft survival continues to remain an elusive goal. Kidney transplant recipients are believed to be at high risk for loss of allograft function, and new, potentially non-nephrotoxic immunosuppressive medications are advocated to improve long-term allograft survival. To evaluate the efficacy of such therapeutic interventions, information regarding the change in GFR among kidney transplant recipients with long-term allograft survival is needed. We studied 40,963 transplant recipients between 1987 and 1996 with allograft survival of at least 2 yr in the United States Renal Data System. Linear regression methods were applied to serial GFR estimates after transplantation. The baseline mean GFR at 6 mo after transplantation was 49.6 ± 15.4 ml/min per 1.73 m^2. During the mean follow-up of 5.7 ± 2.3 yr, the mean $\pm$ standard error of the change in GFR was -1.66 ± 6.51 ml/min per 1.73 m^2 per year (median, -0.94 L/min per 1.73 m^2 per year). A total of 12,583 (30%) of patients had improvement in GFR, 8133 (20%) patients had no change in GFR, and 20,247 (50%) patients had decline in GFR. It is concluded that, although most patients had significant impairment of GFR at baseline, the decline in GFR was slow and many patients had either no change or improvement in GFR. Strategies to improve long-term kidney allograft survival that increase baseline allograft function may be more effective than strategies to slow the decline in GFR.

Long-term allograft survival continues to remain an elusive goal in kidney transplantation. Despite the achievement of acute rejection rates of 15% (1) and 1-yr allograft survival rates of 90% (2), only relatively modest improvements in long-term allograft survival have been recognized (3). The withdrawal of potentially nephrotoxic immunosuppressive medications (calcineurin inhibitors) and the use of non-nephrotoxic immunosuppressive medications have been advocated to improve long-term allograft survival (4–6). However, because there is little information regarding the rate of allograft decline among patients with long-term allograft survival, the potential magnitude of benefit from such new therapeutic approaches is uncertain.

Estimated GFR provides a more precise measure of kidney function than serum creatinine measurements alone (7), and monitoring changes in GFR is the recommended method for assessing the progression of kidney disease (8). The rate of change in kidney function has been used to identify patients at increased risk for kidney failure and to assess the safety and efficacy of treatment in patients with native kidney disease (8–10). In most native kidney disease, GFR declines progressively over time, with mean annual rates of decline between 0 and 12.6 ml/min per year; more rapid rates of decline are often seen in patients with lower baseline levels of GFR (8,11–13).

Recent guidelines characterize kidney transplant recipients to be at high risk for progressive loss of kidney function (8). Because rates of change in allograft function have implications for both the design and assessment of new therapeutic strategies to improve long-term allograft function, we performed this study to describe the annualized change in estimated GFR in a large sample of kidney transplant recipients.

Materials and Methods

Study Population

We studied all adult (age, 18 to 70 yr) first, kidney-only transplant recipients between January 1987 and September 1996 with at least 2 yr of allograft survival in the TXUNOS standard analysis file of the United States Renal Data System (USRDS). Study patients had complete follow-up information in the TXFU-UNOS and Patients standard analysis files. We excluded patients with fewer than three serum creatinine measurements in the first two posttransplant years to permit a precise estimate of the change in GFR (14). In addition, patients with an estimated GFR < 10 ml/min per 1.73 m^2 during the first two posttransplant years were excluded because most patients with GFR at this level would return to dialysis (15). Similarly, patients with GFR > 100 ml/min per 1.73 m^2 during the first two posttransplant years were also excluded because such patients are considered at low risk for progression of chronic kidney disease and because the use of GFR prediction equations at higher levels of GFR may be less accurate (8).

Data Sources

The TXUNOS standard analysis file contains the date of transplantation as well as donor and recipient characteristics. The TXFU-UNOS standard analysis file contains serum creatinine measurements at 6 mo after transplantation and then yearly thereafter, as well as information regarding acute rejection episodes. The Patients standard analysis file contains the dates of recipient birth, death, and allograft loss.

Analytical Methods

Patient characteristics were described as frequencies or as the mean ± SD, unless otherwise indicated. Characteristics of study patients were compared with those of excluded patients using the χ^2 test for categorical variables and t test for continuous variables. For each patient, the GFR was estimated serially after transplantation with an equation derived from the Modification of Diet in Renal Disease (MDRD) Study (GFR = $186 \times$ [serum creatinine]$^{(-1.154)} \times$ [patient age]$^{(-0.203)} \times$ [0.742 if female] $\times$ [1.212 if black]) (16) as recommended by recent guidelines (8). All available serum creatinine measurements recorded in the period beginning 6 mo after the time of transplantation and ending with death, allograft failure, or study end (September 9, 1998) were included in the serial GFR estimates. For patients who returned to dialysis or received a repeat transplant, a GFR of 10 ml/min per 1.73 m^2 was imputed on the date of allograft failure. We wanted a conservative estimate of kidney function at the time of allograft failure; we therefore chose a value that is higher than the mean value of GFR at which patients return to dialysis after transplant failure (8.4 ml/min per 1.73 m^2) (15).

For each patient, the annualized change in GFR was determined by applying linear least squares regression to all available GFR estimates beginning 6 mo after the time of transplantation. The frequency of patients who showed decline (change in GFR ≥ -1.0 ml/min per 1.73 m^2 per year), no change (change in GFR between -1.0 and 1.0 ml/min per 1.73 m^2 per year), and improvement in GFR (increase in GFR ≥ 1.0 ml/min per 1.73 m^2 per year) was determined. The mean ± SEM of the annualized change in GFR was determined in different patient groups, and group differences were tested with simple linear regression. All factors associated with a change in GFR in the simple linear regression analysis ($P < 0.05$) were included in a multivariate regression to determine the independent association of factors with a change in GFR. The following factors were considered: recipient age, gender, race (black/non-black), primary diagnosis (glomerulonephritis, diabetes, polycystic kidney disease, hypertension, other), donor age, donor type (cadaveric/live donor), HLA match, percent panel reactive antibodies, acute rejection within the first three posttransplant months, delayed allograft function (dialysis within first posttransplant week), GFR at 1 yr after transplantation, transplant year, and duration of follow-up. Cook's distance was used to identify points of influence, and the tolerance statistic was used to detect collinearity between independent variables considered in the multivariate regression analysis (17,18).

For patients with GFR estimates available beyond 2 yr after the date of transplantation, piece-wise linear regression (19) was used to determine the annualized change in GFR before and 2 yr after transplantation. The goodness of fit test was used to compare the performance of the linear and piece-wise regression analyses. The annual change in GFR before and 2 yr after transplantation was compared with the t test. The frequency of patients who showed decline, no change, and improvement in GFR before and 2 yr after transplantation was determined. Statistical analyses were performed with SAS software version 8.1 (SAS, Cary, NC).

Results

There were 54,582 eligible patients with complete follow-up information available; 11,732 were excluded because they had fewer than three GFR estimates during the first two posttransplant years. An additional 1887 patients were excluded because at least one GFR estimate in the first two posttransplant years was < 10 or > 100 ml/min per 1.73 m^2. Of the remaining 40,963 patients studied, the annualized change in GFR could be determined before and after 2 yr of allograft survival using piece-wise linear regression in 32,647.

Selected characteristics of the study patients and the comparison with excluded patients are shown in Table 1. The study patients and excluded patients had clinically similar demographic characteristics. In study patients, the baseline GFR (measured at 6 mo after the time of transplantation) was 49.6 ± 15.4 ml/min per 1.73 m^2. Patients were followed for 5.7 ± 2.3 yr (median, 5.3 yr) from the time of transplantation. There were 5458 patients (13%) who returned to dialysis or received repeat transplants after allograft failure, and there were 4397 patients (11%) who died with allograft function. The median number of GFR estimates used to calculate the annualized change in GFR was 5 (range, 3 to 11).

Figure 1 shows the distribution of annualized change in GFR for all study patients. The annualized change in GFR was $-1.66 ± 6.51$ ml/min per 1.73 m^2 per year (median, -0.94 ml/min per 1.73 m^2 per year). A total of 12,583 (30%) of patients had improvement in GFR, 8133 (20%) patients had no change in GFR, and 20,247 (50%) patients had a decline in GFR.

Figure 2 shows the relationship between the GFR attained at 1 yr after the time of transplantation and the annualized change in GFR. Simple linear regression showed a slightly more rapid decline in GFR among patients with higher levels of GFR at 1

Table 1. Selected patient characteristics in study patients and excluded patients

Factor	Study Patients $n = 40,963$	Excluded Patients $n = 13,619$	P^a
Age (yr)	43	44	0.67
% male	60%	60%	0.52
Race			<0.01
White	75%	72%	
Black	21%	22%	
other	4%	6%	
Cause of ESRD^b			<0.01
glomerulonephritis	34%	32%	
diabetes	21%	21%	
polycystic kidney disease	9%	8%	
other	20%	23%	
hypertension	15%	16%	
Cadaveric donor	72%	70%	<0.01

^{a} From t test for continuous variables and χ^2 test for categorical variables.

^{b} ESRD, end-stage renal disease.
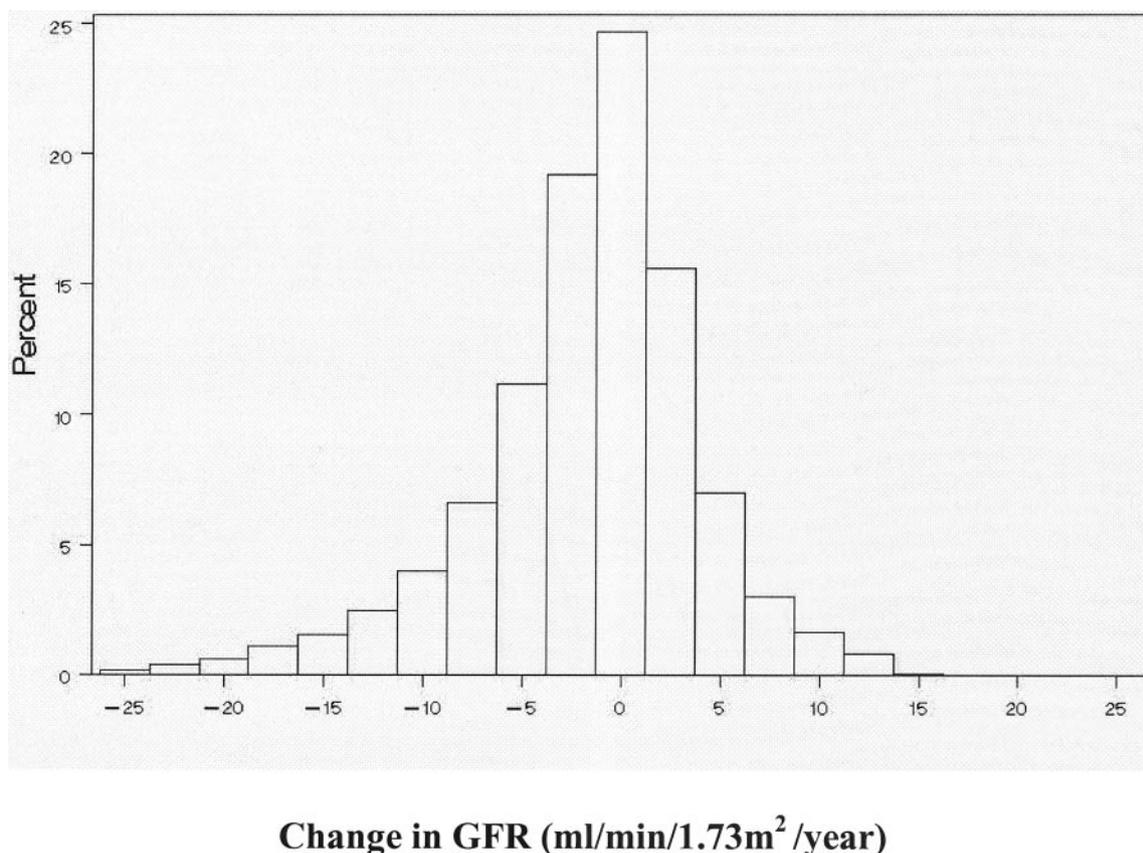
Change in GFR (ml/min/1.73m² /year)

Figure 1. Change in GFR after kidney transplantation. $n = 40{,}963$ transplant recipients between 1987 and 1996 in the United States. The mean $\pm$ SEM of the change in GFR was -1.66 ± 6.51 ml/min per 1.73 m².

yr (for each 10 ml/min per 1.73 m² increase in GFR, the rate of decline in GFR increased by 0.3 ml/min per 1.73m² per yr; $P < 0.01$). Similar results were obtained when the GFR at 6 mo after transplantation was used as the reference point (data not shown).

Table 2 shows the results of the piece-wise linear regression analysis. The mean decline in GFR 2 yr after transplantation (-2.68 ± 9.44 ml/min per 1.73 m² per year) was more rapid than that in the first two posttransplant years (-0.33 ± 8.87 ml/min per 1.73 m² per yr; $P < 0.01$). Table 3 shows the frequency of patients in whom GFR declined, improved, or showed no change before and 2 yr after transplantation. During the first 2 yr, the majority (55%) of patients in whom the change in GFR could be calculated before and 2 yr after transplantation had either no change (11%) or an improvement in GFR (44%). Even 2 yr after transplantation, only 52% of patients had a decline in GFR. Results from goodness of fit tests demonstrated that the performance of the more complex piece-wise linear regression was similar to that from the linear least squares regression (results not shown); therefore, results from the piece-wise progression are not further presented in this report.

Table 4 shows the adjusted annualized change in GFR from the multivariate analysis. Factors associated with a more rapid decline in GFR included younger recipient age, female gender, black race, primary diagnosis other than polycystic kidney disease, older donor age, cadaveric donor source, HLA mismatch, presence of panel reactive antibodies, acute rejection, a higher GFR at 1 yr after transplantation, and shorter duration of follow-up.

Discussion

The excellent short-term outcomes in kidney transplantation have created the need for more meaningful markers of treatment efficacy among recipients with long-term allograft survival. We describe the annualized change in GFR after kidney transplantation among patients with allograft survival of at least 2 yr in the United States. Despite significant impairment of baseline kidney function, there was a slow decline in GFR (-1.66 ± 6.51 ml/min per 1.73 m² per year). Over a median follow-up of nearly 6 yr, only 50% of patients lost kidney function after transplantation, whereas 20% had no change and 30% had improvement in GFR.

The slow rate at which kidney function was lost suggests that the duration of allograft survival is primarily determined by the level of function attained after transplantation; therefore, strategies to improve baseline allograft function may improve long-term allograft survival to a greater extent than strategies to delay the loss of allograft function. Our findings question the recent conclusions from the K-DOQI work group on chronic kidney disease that characterize transplant recipients to be at high risk for loss of kidney function (8). Those conclusions
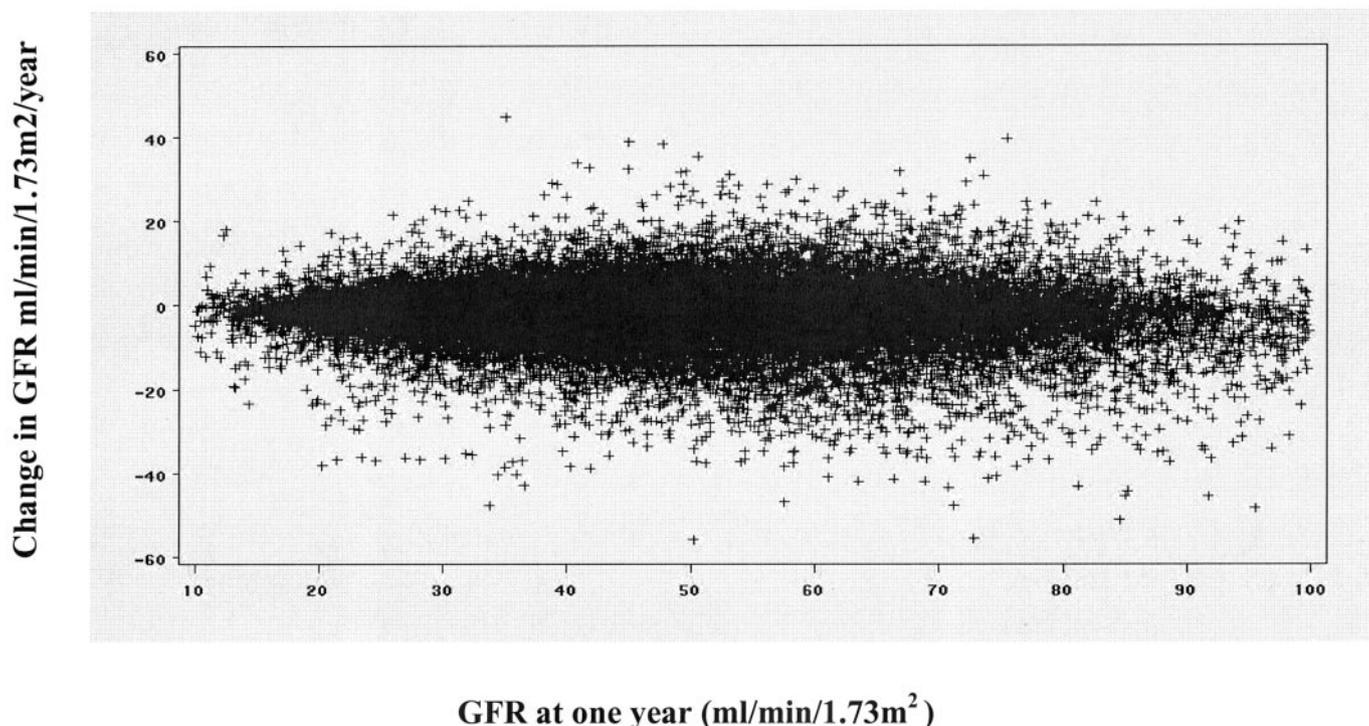
Figure 2. Relationship between GFR at 1 yr after transplantation and change in GFR. For each 10 ml increase in GFR at 1 yr after transplantation, there was a loss of GFR of 0.3 ml/min per 1.73 m^2 per year ($P < 0.001$).

Table 2. Annualized change in GFR (ml/min per 1.73 m^2 per year) before and 2 yr after transplantation (piece-wise regression)

Overall	-1.66 ± 6.51
During first 2 posttransplant years	-0.33 ± 8.87
After first 2 posttransplant years	-2.68 ± 9.44

were based on the expected duration of allograft survival but did not account for the relatively low baseline GFR achieved by most kidney transplant recipients (15).

The mean GFR at 6 mo after the time of transplantation in this cohort of patients was 48.7 ± 15.6 ml/min per year among cadaveric donor recipients and 51.8 ± 14.5 ml/min per year among live donor recipients. Assuming that the mean annualized decline in GFR remains constant and that return to dialysis occurs at 10 ml/min per 1.73 m^2, the expected allograft survival would be approximately 22.5 yr for cadaveric donor recipients and 27.3 yr for live donor recipients. These estimates are consistent with published estimates of allograft survival (11.0 to 19.0 yr for cadaveric donors and 16.9 to 35.9 yr for live donors) (3).

The change in annualized GFR in this study is representative of chronic changes in allograft function, beginning 6 mo after the time of transplantation; therefore, the change in GFR reported here does not reflect the effect of most acute rejection episodes and early posttransplant events on allograft function. As such, we believe that comparisons to other nontransplant populations with chronic kidney disease are relevant. Com-

pared with the cohort of nondiabetic patients with chronic kidney disease who had comparable baseline levels of GFR in the MDRD Study (mean annualized decline in GFR 4 ml/min per year) (20), the transplant recipients in this analysis had a much slower decline in GFR. The slower decline in GFR in transplant recipients suggests that different mechanisms may underlie the progression of chronic kidney disease in native and transplant kidneys.

Thirty percent of patients in this study had an improvement in GFR > 1 ml/min per 1.73 m^2 per year. In comparison, approximately 15% of patients in the MDRD study experienced improvement or stabilization of GFR (20). It is known that allograft mass increases and that there is radiologic evidence of allograft enlargement for approximately 6 mo after the time of transplantation (21). This increase in allograft size is probably due to hypertrophy of individual nephrons secondary to an increase in single nephron GFR. Such physiologic adaptations may also contribute to the improvement of GFR after transplantation. Other factors including a decrease in calcineurin inhibitor dose after transplantation, and the discontinuation of medications such as trimethoprim-sulfamethoxazole may also have contributed to the improvement in GFR.

We found that patients with a higher baseline GFR had a small but significantly more rapid decline in GFR. In nontransplant patients, most studies report a faster rate of progression among individuals with a lower baseline GFR (12,22–24), perhaps because of injury due to hyperfiltration in remaining nephrons (25). Although linear models often accurately represent decline in GFR decline among nontransplant patients with

Table 3. Relationship between change in GFR before and 2 yr after kidney transplantation

Change in GFR during First 2 Posttransplant Years	Change in GFR 2 yr after Transplantation
Decline: 45% ($n = 14,638$)[a]	Decline 47%
	No change 19%
	Improved 34%
No change: 11% ($n = 3562$)[b]	Decline 48%
	No change 22%
	Improved 30%
Improved: 44% ($n = 14,447$)[c]	Decline 57%
	No change 18%
	Improved 25%

[a] Loss of GFR ≥ -1.0 ml/min per 1.73 m^2 per year.
[b] Change in GFR between -1.0 and 1.0 ml/min per 1.73 m^2 per year.
[c] Increase in GFR >1.0 ml/min per 1.73 m^2 per year.

Table 4. Adjusted annualized change in GFR[a] (multivariate regression)

	Adjusted Annualized Change in GFR (regression coefficient $\pm$ SEM)[b]	P[bc]
Recipient age (per decade older)	0.67 ± 0.02	<0.001
Female gender	-0.67 ± 0.06	<0.001
Black race (reference, non-black)	-1.57 ± 0.08	<0.001
Cause of kidney disease (reference polycystic disease)		
GN	-0.69 ± 0.12	<0.001
other	-0.54 ± 0.12	<0.001
diabetes	-0.96 ± 0.12	<0.001
hypertension	-0.80 ± 0.13	<0.001
Donor age (per decade older)	-0.32 ± 0.02	<0.001
Cadaveric donor (reference, live donor)	-0.57 ± 0.07	<0.001
Zero HLA mismatch (reference, HLA mismatch 1–6)	0.80 ± 0.10	<0.001
No panel reactive antibodies (reference, any)	0.35 ± 0.06	<0.001
Delayed allograft function (reference, no)	-0.07 ± 0.08	0.40
Acute rejection in first 3 mo (reference, no)	-0.53 ± 0.07	<0.001
GFR at 1 yr after transplant (per 10 ml/min per 1.73 m^2 higher)	-0.40 ± 0.02	<0.001
Duration of follow-up (per year longer)	0.52 ± 0.14	<0.001

[a] ml/min per 1.73 m^2 per year.
[b] Regression coefficients and SEM calculated from a multivariate regression to determine factors associated with a change in annualized GFR that included all of the variables shown.
[c] P value refers to the coefficients in the multivariate analysis.

chronic kidney disease (26,27), other studies have shown that other relationships (piece-wise regression or spline) may also be appropriate (28). We explored this possibility in our study and found that the piece-wise and linear regression methods performed similarly in kidney transplant recipients. The significantly more rapid decline in GFR 2 yr after transplantation is related to the fact that any graft failures in the study patients occurred after the first two posttransplant years. Among those who lost kidney function, GFR decline varied widely. This underscores the fact that multiple processes (immunologic and non-immunologic) may contribute to loss of kidney function in this population.

The multivariate analyses demonstrated that many donor, recipient, and immunologic characteristics were associated with more rapid decline of GFR. These observations are consistent with previous studies showing the association of many of these factors (female gender, black race, older donor age, cadaveric donor source, delayed graft function, and acute rejection) with the duration of allograft survival (3,29) The association of HLA match and panel reactive antibodies with the change in GFR suggests that immune mechanisms continue to have an effect on allograft function even among the long-term transplant recipients in this study.

We included the duration of follow-up rather than an indi-

cator of transplant year in the multivariate analysis because this variable not only accounts for an era effect due to improvements in immunosuppression and general patient care that have occurred over time, but it also accounts for any survivor bias among patients with the longest duration of follow-up. Patients with longer duration of follow-up had a less rapid decline in GFR, and this effect was more important than any era effect that we found in alternative models that included transplant year (data not shown). Because of the retrospective nature of our study, we could not determine the effect of many potentially modifiable clinical factors that have been associated with progression of native kidney disease (*e.g.*, hypertension, proteinuria, and anemia) on the rate of decline in allograft function.

There are a number of issues that should be considered when interpreting the results of our study. We included only patients with allograft survival of at least 2 yr to ensure precise estimates of the change in allograft function. Although excluding patients with early allograft loss probably reduced our estimate of the decline in GFR among all kidney transplant recipients, allograft loss in the excluded patients was unlikely to have been due to progression of chronic disease, which was the focus of this study.

The precision of the estimate of the change in GFR in this study is dependent on a number of factors, including the number of measurements of GFR, the duration of patient follow-up, error in the measurement or recording of serum creatinine, and error in the estimation of GFR. In the multivariate analysis, patients with a longer duration of follow-up had a less rapid decline in GFR. However, all patients in this study had at least three GFR measurements, and the median follow-up in this study is longer than most studies of GFR decline in the nontransplant population (30,31). We estimated kidney function using an equation derived from the MDRD study (16) that has been recommended for use in all patients with chronic kidney disease, including kidney transplant recipients (8). In our opinion, equations derived from the MDRD study offer several theoretical advantages that may decrease the error associated with estimating GFR. These include the use of a validated method of measuring GFR (kidney clearance of iothalamate) to derive the equation and the use of the most widely accepted method to measure serum creatinine in the United States (alkaline picrate) (32). However, similar to other equations that predict GFR, the MDRD equation has not been specifically validated in a large population of transplant recipients and its accuracy in transplant recipients has been questioned (33,34).

In summary, this study describes the change in GFR among a large cohort of transplant recipients in the United States with allograft survival of at least 2 yr. The mean decline in GFR in this study was lower than in most studies of GFR decline in nontransplant populations. Because GFR decline after transplantation was relatively slow in the majority of patients, strategies to increase allograft survival by improving the baseline level of allograft function may be more effective than strategies to slow the progression of chronic kidney disease in kidney transplant recipients.

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