Transplantation

Influence of Donor's Renal Function on the Outcome of Living Kidney Transplantation: 10-Year Follow-up

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Purpose: With the improved surgical techniques and immunosuppression available today, conventional prognostic factors have taken on less significance. Accordingly, the native renal function of the donor is thought to be more important. Thus, we analyzed the prognostic significance of the donor's renal function as assessed by 24-hour urine creatinine clearance on kidney graft survival for 10 years after living kidney transplantation.

Materials and Methods: From January 1998 to July 2000, 71 living kidney transplantations were performed at a single institution. From among these, 68 recipients were followed for more than 6 months and were included in the present analysis. We analyzed kidney graft survival according to clinical parameters of the donor and the recipient.

Results: Mean follow-up duration of recipients after living kidney transplantation was 115.0 ± 39.4 months (range, 10 to 157 months), and 31 recipients (45.6%) experienced kidney graft loss during this time period. Estimated mean kidney graft survival time was 131.8 ± 6.2 months, and 5-year and 10-year kidney graft survival rates were estimated as 88.2% and 61.0%, respectively. Donor's mean 24-hour urine creatinine clearance (Ccr) before kidney transplantation was 122.8 ± 21.2 ml/min/1.73 m² (range, 70.1 to 186.6 ml/min/1.73 m²). The 10-year kidney graft survival rates for cases stratified by a donor's Ccr lower and higher than 120 ml/min/1.73 m² were 39.0% and 67.2%, respectively ($p=0.005$). In univariate and multivariate analysis, donor's Ccr was retained as an independent prognostic factor of kidney graft survival ($p=0.001$ and 0.005, respectively).

Conclusions: Donor's 24-hour urine Ccr before living kidney transplantation was an independent prognostic factor of kidney graft survival. Therefore, it should be considered before living kidney transplantation.

Key Words: Creatinine; Kidney transplantation; Survival

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INTRODUCTION

Kidney transplantation (KT) is one of the treatments widely used for patients with end-stage renal disease. KT is considered the best therapeutic method in patients with end-stage renal disease because of the increased life expectancy of the recipients [1].

The factors known to influence the survival of the trans-

planted kidney in living KT patients are as follows: the donor's age, the level of human leukocyte antigen (HLA) histocompatibility, acute rejection, and the type of immunosuppressive drugs used [2-8]. However, with the improved surgical techniques and effective immunosuppression available today, conventional prognostic factors have taken on less significance [2]. Accordingly, the native renal function of the donor is thought to be more important.

The most objective and universal index of renal function is the glomerular filtration rate (GFR), which measures the amount of blood plasma filtered from the glomerulus in the unit of time (ml/min). The GFR is measured by the creatinine clearance (Ccr) from the urine collected for 24 hours. To the best of our knowledge, no study to date has investigated the relationship between the donor's 24-hour urine Ccr before KT and the recipient's kidney graft survival (KGS) after surgery.

Therefore, on the basis of 10-year follow-up results after surgery, we tried to determine how the 24-hour urine Ccr of the donor, measured before living KT, can influence the KGS of the recipient after surgery.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Hallym University, Chuncheon Sacred Heart Hospital. A total of 71 patients who underwent living KT performed by single surgeon were recruited from a single institution from January 1998 to July 2000. Sixty-eight of the 71 recipients were retrospectively included in this study according to the following criteria: the donor's 24-hour urine Ccr was measured before KT, the patient was followed for more than 6 months, KGS was verified, and the patient did not undergo re-operation. Clinical data were retrospectively reviewed. The following parameters were recorded in each case: the donor's age and gender, the recipient's age and gender, blood relationship, the donor's 24-hour urine Ccr before KT, the recipient's 24-hour urine Ccr and KGS at follow-up, acute rejection, HLA and HLA-DR matching, and drugs used for immune suppression.

The recipients with kidney graft loss or who were followed up for less than 6 months after KT were excluded from our study because their KGS was associated with increased perioperative morbidity or mortality. Renal function was assessed by GFR by use of 24-hour urine Ccr according to the formula:

24-hour urine Ccr = urine creatinine / urine volume / plasma creatinine.

All values for 24-hour urine Ccr were measured during hospitalization and were corrected on the basis of the body surface area to millimeter per minute per 1.73 m^2 for exact and objective outcomes. Acute rejection was confirmed through kidney biopsy in patients with clinical abnormalities, such as decreased urine output or serum creatine level increased by 25% or higher. Kidney graft loss was defined as either 'dialysis in need' or 'death associated with renal failure' but not as 'death with a functioning graft.' Triple therapy was applied for immunosuppressive therapy, and cyclosporine was used as the main immunosuppressive drug. Corticosteroid therapy was used in all recipients, and azathioprine and mycophenolate mofetil were used in 30 and 38 recipients, respectively.

SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The cutoff value for donor's 24-hour urine Ccr was calculated by the minimum p-value

approach and corrected by the Bonferroni correction method. The Kaplan-Meier method was used to analyze KGS, and the log-rank test was used to compare the investigated groups. The prognostic values of parameters were evaluated by using both univariate and multivariate Cox proportional hazards models. All p-values were two-sided, and $p < 0.05$ was considered to be statistically significant.

RESULTS

The recipients' mean age was 36.8 years (range, 20 to 59 years), and there were 37 males (54.4%). The most common primary cause of end-stage renal disease was glomerulonephritis (13 recipients, 19.1%). After KT, the mean duration of the follow-up period was 115.0 ± 39.4 months (range, 10 to 157 months). The mean 24-hour urine Ccr levels of the surviving recipients, measured at 1, 5, and 10 years after KT, were 69.8 ± 16.0 (67 recipients), 63.5 ± 22.6 (60 recipients), and $59.9 \pm 34.2 \text{ ml/min/1.73 m}^2$ (38 recipients), respectively.

The donors' mean age was 35.9 years (range, 21 to 58 years), and there were 42 males (61.8%). Thirty donors (44.1%) were related to the recipients. The mean 24-hour urine Ccr level of the donors measured before KT was $122.8 \pm 21.2 \text{ ml/min/1.73 m}^2$. There were 21 cases of acute rejection (30.9%) (Table 1).

During the follow-up period, there were 31 cases (45.6%) of graft loss after KT. The mean KGS time of the recipients was 131.8 ± 6.2 months, and the estimated 5-year and 10-year KGS rates were 88.2% and 61.0%, respectively.

The optimal cutoff value for donor's 24-hour urine Ccr was $120.05 \text{ ml/min/1.73 m}^2$ ($p < 0.001$, sensitivity 86.5%, specificity 35.5%). Therefore, $120 \text{ ml/min/1.73 m}^2$ was determined as the cutoff value. When the donor's 24-hour urine Ccr before KT was divided into less than $120 \text{ ml/min/1.73 m}^2$ ($n=16$) and greater than $120 \text{ ml/min/1.73 m}^2$ ($n=52$), the mean KGS time of each group was 96.0 ± 9.6 months and 139.5 ± 6.8 months, respectively ($p=0.005$). The estimated 10-year KGS rate of each group was 39.0% and 67.2%, respectively (Fig. 1).

The results of the univariate analysis showed that the 24-hour urine Ccr of the donor before KT was a significant risk factor of kidney graft loss ($p=0.001$, hazard ratio [HR], 0.163). In the multivariate analysis, the 24-hour urine Ccr of the donor before KT remained an independent risk factor of kidney graft loss when corrected for all other variables ($p=0.005$, HR, 0.143) (Table 2).

DISCUSSION

KT is the best therapeutic method for patients with end-stage renal disease and has shown significant long-term outcomes. In about 800 cases of living KT investigated between 1991 and 2001, Foster et al. [9] reported that the 5-year KGS rate ranged from 82.9 to 89.1%. Using the United Network for Organ Sharing registry, between 1998 to 2001, Cecka [10] analyzed 14,162 cases of living KT and

TABLE 1. Characteristics of the donors and recipients

Characteristic	Overall (n=68)	Group A (n=16)	Group B (n=52)	p-value
Age (yr), mean (SD)				
Donor	35.9 (9.4)	37.8 (8.6)	35.3 (9.6)	0.356
Recipient	36.8 (9.2)	34.9 (10.3)	37.3 (8.8)	0.369
Male sex, n(%)				
Donor	42 (61.8)	7 (43.8)	35 (67.3)	0.090
Recipient	37 (54.4)	9 (56.3)	28 (53.8)	0.866
Primary cause of ESRD, n(%)				^b
Glomerulonephritis	13 (19.1)	3 (18.8)	10 (19.2)	
Diabetes	10 (14.7)	1 (6.3)	9 (17.3)	
Hypertension	7 (10.3)	2 (12.5)	5 (9.6)	
Others	38 (55.9)	10 (62.5)	28 (53.8)	
Donor's Ccr before KT, mean (SD) ^a	122.8 (21.2)	95.7 (17.1)	131.1 (14.2)	<0.001
Recipient's Ccr at 10 years after KT, mean (SD) ^a	59.9 (34.2)	28.3 (37.7)	69.7 (26.6)	<0.001
Relation, n(%)				
Related	30 (44.1)	9 (56.3)	21 (40.4)	0.352
Offsprings	3 (4.4)	1 (6.3)	2 (3.8)	
Parents	4 (5.9)	2 (12.5)	2 (3.8)	
Siblings	23 (33.8)	6 (37.5)	17 (32.8)	
Unrelated	38 (55.9)	7 (43.7)	31 (59.6)	0.058
Acute rejection, n(%)	21 (30.9)	8 (50.0)	13 (25.0)	0.198
HLA matching, n(%)				
1-3	63 (92.6)	16 (100)	47 (90.4)	0.678
4-6	5 (7.4)	0 (0)	5 (9.6)	
HLA-DR matching, n(%)				
0-1	62 (91.2)	15 (93.8)	47 (90.4)	0.801
2	6 (8.8)	1 (6.2)	5 (9.6)	
Immunosuppression, n(%)				
CS, PD, AZT	30 (44.1)	7 (43.7)	23 (44.2)	
CS, PD, MMF	38 (55.9)	9 (56.3)	29 (55.8)	

Group A: Donor's Ccr before KT ≤ 120 ml/min/1.73 m², Group B: Donor's Ccr before KT > 120 ml/min/1.73 m².

ESRD, end stage renal disease; Ccr, 24-hour urine creatinine clearance; KT, kidney transplantation; HLA, human leukocyte antigen; n, cases; SD, standard deviation; CS, cyclosporin; PD, prednisolone; AZT, azathioprine; MMF, mycophenolate mofetil.

^a: Ccr unit: ml/min/1.73 m², ^b: no statistical analysis.

FIG. 1. Kaplan-Meier curve for kidney graft survival of recipients according to donor's Ccr before kidney transplantation. Ccr, 24-hour urine creatinine clearance.

reported that the 10-year KGS rate was 68%. In our study, between 1998 and 2000, the recipient's 5- and 10-year KGS

rates of 88.2% and 61.0%, respectively, were similar to those reported in the previous studies.

Many studies have reported that the donor's age, acute rejection, the level of HLA antigen histocompatibility, and the type of immunosuppressive drugs are risk factors that influence the KGS rate [2-8]. However, with improved surgical technologies and the prevention of postoperative complications and the development of new immunosuppressive drugs, the KGS rate has increased from the late 1980s, and the conventional prognostic factors have taken on less significance [2]. Therefore, the native renal function of the donor is thought to be more important for the KGS rate after surgery.

Among the various indices of renal function, the most objective and universal index is the GFR, which is measured by the 24-hour urine Ccr. The donor's renal function, as measured by the serum creatinine, not Ccr, was assessed in previous studies [11]. To the best of our knowledge, this is the first study investigating the influence of the donor's 24-hour urine Ccr, measured before living KT, on the KGS rate after surgery.

TABLE 2. Univariate and multivariate analyses predicting probability of kidney graft survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Recipient's gender						
Female sex	1.013	0.340-3.016	0.982	1.104	0.270-4.516	0.891
Recipient's age	0.954	0.894-1.018	0.158	0.950	0.882-1.022	0.170
Donor's gender						
Female sex	0.706	0.217-2.292	0.562	0.232	0.050-1.073	0.062
Donor's age	1.030	0.977-1.086	0.276	1.025	0.948-1.109	0.530
Relation			0.879			0.402
Sibling vs. parent/offspring	1.513	0.177-12.956	0.705	4.521	0.270-75.597	0.294
Unrelated vs. parent/offspring	1.170	0.144-9.511	0.883	1.555	0.134-18.118	0.724
HLA matching						
4-6 vs. 1-3	0.043	0.001-219.067	0.471	0.000	0.000	0.988
HLA-DR matching						
2 vs. 0-1	0.734	0.095-5.647	0.766	3.186	0.253-40.082	0.370
Acute rejection	3.359	1.125-10.025	0.030	4.790	1.265-18.134	0.021
Immunosuppression						
CS, PD, MMF vs. CS, PD, AZT	0.952	0.082-8.216	0.871	0.998	0.035-15.341	0.890
Donor's Ccr						
≥ 120	0.163	0.053-0.495	0.001	0.143	0.037-0.557	0.005

HR, hazard ratio; CI, confidence interval; HLA, human leukocyte antigen; CS, cyclosporin; PD, prednisolone; MMF, mycophenolate mofetil; AZT, azathioprine; Ccr, 24-hour urine creatinine clearance.

Lee et al. [12] reported that the mean recipient's 24-hour urine Ccr level showed a 141.5% increase at 1 week after KT, although they did not assess the long-term renal function change. They stated that the residual function of the recipient's native kidney function measured before KT did not show much correlation with the recipient's renal function after KT. This means that the transplanted kidney function decides most of the recipient's renal function after KT. Therefore, we thought that one of the most important factors affecting KGS was the donor's renal function measured before KT, as assessed by the 24-hour urine Ccr.

We considered the donor's 24-hour urine Ccr value of 120 ml/min/1.73 m² as a division point. This was calculated by the minimum p-value approach compensated by the Bonferroni correction method ($p < 0.001$). When the donor's 24-hour urine Ccr level before living KT was divided into less than 120 ml/min/1.73 m² and above this cutoff, the 10-year KGS rates for each group were 39.0% and 67.2%, respectively ($p = 0.005$). The donor's 24-hour urine Ccr level before living KT was a significant prognostic factor in the univariate analysis ($p = 0.001$; HR, 0.163) and also in the multivariate analysis, which was corrected for all other variables ($p = 0.005$; HR, 0.143) (Table 2). Therefore, the donor's 24-hour urine Ccr must be measured before living KT and considered as a prognostic factor of KGS.

There are conflicting opinions about the influence of the donor's age on KGS. Kaplan et al. [2] reported that the donor's age was a significant risk factor, i.e., when the donor was older than 18 years, the kidney graft loss rate was increased. However, this result is in all likelihood due to a lesser functional reserve of the kidney, along with age-related injury, decreasing the kidney's ability to withstand

further damage. Park et al. [8] reported that the donor's age was not related to KGS in 57 months of follow-up after KT. Our study also showed no correlation between the donor's age and KGS.

Blood relationship between donor and recipient was considered to be an important risk factor in the past [13], but not in recent studies. Park et al. [8] reported that blood relationship was not a significant risk factor, and Kaplan et al. [2] stated that the advantage of living donor kidneys held equally true for unrelated donors. Blood relationship was not considered as a significant risk factor in our study, and we consider that transplanted kidneys with good renal function are more important than blood relationship.

With the improved immunosuppression available today, HLA matching has taken on less significance, although this is still considered to be an important prognostic factor [2,14]. It was not considered as a significant risk factor in our study. However, it is difficult to determine its significance with statistic values only, because our result did not have a high confidence level. This is one of the weak points of our study.

Many studies have considered acute rejection as an important risk factor for KGS [2,15]. In our study, the number of recipients with acute rejection differed between the two groups, although there was no statistical difference. It was thought that the difference in HLA matching was one reason for this difference. In the multivariate analysis, it was also an important risk factor, and the kidney graft loss rate was 4.79 times higher when there was acute rejection. Therefore, acute rejection is considered to be an important risk factor that determines KGS, together with the donor's 24-hour urine Ccr measured before KT.

A few studies showed that different immunosuppressive drugs make a difference in the long-term outcome [2,14,15]. Both the short-term outcome and the acute rejection rate were improved, but the long-term outcome did not improve much. In our study, type of immunosuppressive drug was also not considered as a risk factor.

There are a few limitations in our study. First, our study followed a retrospective design. Therefore, several variables, such as newly developed immunosuppressive drugs or interleukin-2 antibody, which may better reflect clinical outcomes, were not included in the analyses [16,17]. Second, although our study continuously followed up on the recipients after KT, the 24-hour urine Ccr was not measured on a regular basis for all recipients. However, our study included most of the conventional variables associated with KGS, and we studied recipients for 10 long years. Third, other indices of renal function, such as the 24-hour albuminuria or more currently accepted iothalammic clearance test, need to be assessed. Last, the number of cases in our study was relatively smaller than in previous studies, although we followed the patients for 10 years.

Despite these limitations, our study is significant as the first report on the influence of the donor's 24-hour urine Ccr measured before living KT, which is the most objective and universal index of renal function, on KGS. In the future, as surgical technology and immunosuppressive drugs are developed and the rates of KGS rise, the influence of the donor's renal function on KGS will increase.

CONCLUSIONS

The renal function of the donor measured before living KT, using the 24-hour urine Ccr, was a significant prognostic factor influencing KGS. The objective renal function of the donor needs to be evaluated for living KT, and it should be considered before living KT.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Evans RW, Manninen DL, Garrison LP Jr, Hart LG, Blagg CR, Gutman RA, et al. The quality of life of patients with end stage renal disease. *N Engl J Med* 1985;312:553-9.
2. Kaplan B, Srinivas TR, Meier-Kriesche HU. Factors associated with long-term renal allograft survival. *Ther Drug Monit* 2002;24:36-9.
3. Palomar R, Ruiz JC, Zubimendi JA, Cotorruelo JG, de Francisco AL, Rodrigo E, et al. Acute rejection in the elderly recipient: influence of age in the outcome of kidney transplantation. *Int Urol Nephrol* 2002;33:145-8.
4. Busson M, N'Doye P, Benoit G, Hannoun L, Adam R, Pavie A, et al. Donor forctors influencing organ transplant prognosis. *Transplant Proc* 1995;27:1662-4.
5. Kwak JY, Kwon OJ, Lee KS, Kang CM, Park HY, Kim JH. Exchange-donor program in renal transplantation; a single-center experience. *Transplant Proc* 1999;31:344-5.
6. Benoit G, Bensadoun H, Moukarzel M, Richard C, Castaing D, Izard V, et al. Influence of donor age on graft function in a single procurement center. *Transplant Proc* 1990;22:358.
7. Lee CK, Im H, Park SU, Lee SD, Kim JC, Rhew HY. Clinical analysis of 300 renal transplantations. *Korean J Urol* 1995;36:91-8.
8. Park CG, Lee JJ, Park HY. Donor factors influencing the graft survival of kidney transplants. *Korean J Urol* 1999;40:1355-9.
9. Foster CE 3rd, Philosophe B, Schweitzer EJ, Colonna JO, Farney AC, Jarrell B, et al. A decade of experience with renal transplantation in African-Americans. *Ann Surg* 2002;236:794-804.
10. Cecka JM. The UNOS renal transplant registry. *Clin Transpl* 2002;1-20.
11. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002;74:1281-6.
12. Lee SR, Yoon SN, Lee BM, Oh CK, Kim SJ, Kim H, et al. Changes of glomerular filtration rate of donated and remnant kidneys in a week after living donor kidney transplantation. *J Korean Soc Transplant* 2006;20:55-62.
13. Takiff H, Mickey MR, Cicciarella J, Terasaki PI. Factors important in ten-year kidney graft survival. *Transplant Proc* 1987;19:666-8.
14. Taylor CJ, Welsh KI, Gray CM, Bunce M, Bayne AM, Sutton PM, et al. Clinical and socioeconomic benefits of serological HLA-DR matching for renal transplantation over three eras of immunosuppression regimens at a single unit. *Clin Transpl* 1993;233-41.
15. Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, Persson NH. The impact of acute rejection episodes on long-term graft function and outcome in 1349 primary renal transplants treated by 3 cyclosporine regimens. *Transplantation* 1993;26:307-15.
16. Tiong HY, Goldfarb DA, Kattan MW, Alster JM, Thuita L, Yu C, et al. Nomograms for predicting graft function and survival in living donor kidney transplantation based on the UNOS registry. *J Urol* 2009;181:1248-55.
17. Kaplan B. Overcoming barriers to long-term graft survival. *Am J Kidney Dis* 2006;47(4 Suppl 2):S52-64.