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Living related kidney donors over 60 years old

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Abstract The lack of available cadaveric organs for transplantation has resulted in an increased number of kidney transplants from living donors. During a period of 6 years, 149 kidney transplantations were performed from living related donors in our institute, 33.5 % of whom were older than 60 years of age. In this study we examined the survival of patients and grafts as well as the graft function in 50 patients with transplants from donors over 60 years (mean age 65 years) as compared with those of 99 patients with transplants from donors younger than 60 years (mean age 47 years). There were no significant differences in the course of donor nephrectomy, postoperative complications, or remnant kidney function. However, delayed graft function occurred more frequently in recipients of transplants from older donors. Improvement in graft function was also slower in recipients of kidneys from older donors, with significant differences in serum creatinine levels observed during the first 12 months after transplantation. More frequent acute complications and more progressive chronic graft failure, irrespective of the causes, occurred during the 1st post-transplant year in recipients with grafts from older donors. Five-year patient survival (77 % vs 92 %) and kidney graft survival differed significantly for the same period with worse results for patients receiving grafts from older donors. It may be concluded that kidney grafts from donors older than 60 years – and especially those older than 70 years – may be used for living related kidney transplantation, but with precautions.

Key words Kidney transplantation, elderly donors · Advanced age donors, kidney transplantation · Elderly donors, kidney transplantation · Living related kidney transplantation, donor age

Introduction

Since 1987 the number of kidney transplantations has remained constant in spite of intensive efforts to increase it [2, 9]. Two growing number of dialysis patients by far exceeds the rate at which kidney transplantations are being performed [2, 9]. To harvest available kidneys for transplantation, increasing the percentage of living related donors to include those over 60 years of age, reducing the minimum criteria for acceptance of a prospective organ, and using good preservation solutions, nonheart-beating donors, anencephalic fetus donors, and unrelated donors or xenotransplantation have all been proposed [1, 2, 9, 19, 25].

A lack of cadaveric kidneys has resulted in an increase in living related kidney transplantations at the Institute for Urology and Nephrology in Belgrade. Between 1987 and 1992, we performed 212 kidney transplantations. One hundred forty-nine (70 %) of these pa-

tients received kidneys from living related donors, 50 of whom (33.5 %) were older than 60 years.

The present retrospective study of transplant patients receiving kidneys from older donors was undertaken with the aim of assessing the influence of donor age on both patient and graft survival as well as on graft function. At the same time, the postoperative course and remnant kidney function of the donors were analyzed.

Patients and methods

Between 1987 and 1992, 50 kidney graft recipients transplanted at our Institute received their first graft from a living related donor older than 60 years of age. These patients formed group 1 (donor age 60–85 years) and were compared to group 2, which consisted of the remaining 99 patients who received grafts from living related donors younger than 60 (donor age 34–59 years). Data on patients studied are presented in Table 1. The underlying kidney diseases in group 1 patients were: chronic glomerulonephritis (GN; $n = 30$), tubulointerstitial nephropathy (TIN; $n = 8$), diabetes mellitus ($n = 2$), polycystic kidney disease ($n = 1$), and unknown ($n = 9$). The underlying kidney diseases in patients in group 2 were: GN ($n = 69$), TIN ($n = 20$), and unknown ($n = 10$). The patient groups were on maintenance hemodialysis for 21 and 18 months, respectively, before kidney transplantation. Donors and recipients were carefully examined according to a standard immunological and clinical procedure at our department. Donor kidney function was normal for both donor groups, and no patient had hypertension or any other disease considered a contraindication for donation and operation.

Initial immunosuppression consisted of antilymphocyte globulin, cyclosporin, azathioprine, and prednisone. When good graft function had been established, cyclosporin was started in a daily dose of 10 mg/kg of body weight orally. Maintenance triple immunosuppressive therapy was administered to the majority of patients (45 from group 1 and 94 from group 2), while the remaining patients were treated with cyclosporin and prednisone (4 from group 1 and 2 from group 2) or azathioprine and prednisone (1 from group 1 and 3 from group 2).

Graft function was followed 33–60 months after kidney transplantation (i.e., until the last control in September 1995 or until hemodialysis had to be restarted). Graft function was assessed by serum creatinine levels (Jaffe's method). Acute rejection was defined as an increase in serum creatinine by 25 % or more, characteristic ultrasound findings in the presence of low or normal cyclosporin trough levels (< 200 ng/ml), and it was mostly pathohistologically confirmed. In addition, a positive response to immunosuppressive pulse therapy was obligatory in order to establish the diagnosis of rejection. Delayed graft function was defined as a continuous need for hemodialysis postoperatively or, for patients not needing hemodialysis, as a lack of decrease in serum creatinine in the absence of acute rejection and urinary tract or renal graft vessel obstruction. A progressive decline in graft function was said to indicate chronic graft failure. Remnant kidney function of donors was followed for 12 months postdonation.

Data are presented as median values, ranges, and mean ± SEM and were compared using the Mann-Whitney U-test, Student's t-test, and Fischer's test, as appropriate. Patient and graft survival were estimated according to the Kaplan-Meier method [14] and comparison of survival curves using the Lee-Desu statistic. Multivariate comparisons were made using the Cox proportional hazards regression [17].

Table 1 Data on studied donors and recipients

	Group 1	Group 2	P
Donors	50	99	
Age (years)[a]	65.5 ± 3.7	47.6 ± 4.3	0.02
Sex (f/m)	29/21	20/15	NS
Family relationship			
Parent	45	95	
Grandparent	5	0	
Sibling	0	4	
Recipients			
Age (years)[a]	35.8 ± 7.2	26.9 ± 6.5	0.02
Sex (f/m)	25/25	26/73	NS
Difference[b]			
Age (years)[a]	29.9 ± 6.2	21.7 ± 4.7	0.02
Sex	18/50	12/99	NS
ABO mismatches	9/50	4/35	NS
HLA mismatches:			
0/1	7/20	20/27	
2/3		20/3	52/0
PRA (number of patients)			NS
< 50 %	49	99	
> 50 %	1	0	
MLC-R[a,c]	0.42 ± 0.08	0.32 ± 0.06	NS

[a] $\bar{x}$ ± SEM

[b] Difference between recipients and donors

[c] The index of proliferative response in mixed lymphocyte culture (MLC-R) was calculated as follows: cpm in donor + recipient MLC/(cpm in MLC of recipient + unrelated person with maximal stimulation)

Results

From the data presented in Table 1 one can see that there were no significant differences between the groups with regard to any donor or recipient characteristics except age: both donors and recipients from group 1 were older than those from group 2 ($P = 0.02$). Furthermore, the age difference between donors and recipients was higher in group 1 than in group 2 ($P < 0.02$). No significant difference was found in the number of HLA mismatches, percentage of PRA, or proliferative response in mixed lymphocyte culture (MLC-R) for the two groups examined. The underlying kidney disease and period of maintenance hemodialysis were also similar in both recipient groups.

Data on the operation (i.e., donor nephrectomies and transplantations) are presented in Table 2. Warm and cold ischemia times were similar in both groups. More complications during donor nephrectomy were noted in group 1 than in group 2. On the other hand, more early postoperative complications were noted in younger donors, though the difference was not significant (Table 3). The remnant kidney function remained stable in both donor groups during the 1st postoperative year (Table 3). Two older donors died, one 2 months after donor nephrectomy and the other 3 years later. One

Table 2 Data on nephrectomy and kidney transplantation

	Group 1	Group 2	*P*
Complication during donor nephrectomy:			
Aortic damage	2	0	NS
Ischemia time (min)[a]			
Warm	2.05 ± 0.1	1.87 ± 0.1	NS
Cold	46.3 ± 6.8	48.5 ± 5.9	NS
Delayed graft function (number of patients)	12/50	5/99	< 0.01

[a] $\bar{x} \pm$ SEM

Table 3 Follow-up of the donors (*ARF* acute renal failure)

	Group 1	Group 2	*P*
Early complications:			
Phlebothrombosis	2	1	
ARF	0	2	
Pneumonia	0	1	
Peptic ulcer	0	1	
Serum creatinine (μmol/l)[a]			
Predonation	95.04 ± 2.5	89.8 ± 2.5	NS
12 months after donation	104.05 ± 4.1	100.3 ± 7.6	NS

[a] $\bar{x} \pm$ SEM

younger donor died 2 months after donor nephrectomy. Their subjective and objective status as well as remnant kidney function were stable and normal at the last check-up in the outpatient department. The deaths were sudden and the causes unknown.

Delayed graft function occurred in 12 patients in group 1 versus 5 in group 2 ($P < 0.01$; Table 2). The number of acute rejection episodes was greater in group 1 than in group 2 (30 vs 26, $P < 0.05$). Improvement in graft function was slower in recipients transplanted from older donors, with significant differences in median values of serum creatinine levels observed between the groups during the first 12 months after transplantation (Fig. 1). Thereafter, the difference in serum creatinine levels disappeared because the majority of patients with progressive chronic graft failure from group 1 lost their grafts by the end of the 1st post-transplant year (10 of 20 patients with chronic graft failure). Thus, only the patients with normal and slow progressive chronic graft failure from group 1 remained for further follow-up, and their median values of serum creatinine were similar to those from group 2.

Five-year patient and graft survival rates are presented in Fig. 2. Patient survival was worse for group 1 from the 24th postoperative month until the end of the observation period ($P = 0.008$). As can be seen from Table 4, infection was the most common cause of death in both groups studied. Graft functions were preserved in all patients who died.

The actuarial graft survival rate for the first 5 years was 76 %, 62 %, 52 %, 47 %, and 42 % for group 1 and 92 %, 81 %, 73 %, 67 %, and 64 % for group 2 (Fig. 2). Thus, a significantly worse graft survival rate for group 1 than for group 2 was observed during the entire follow-up period ($P = 0.05$ for the first 12 months and $P = 0.001$ until the end of the observation). Furthermore, a Cox model analysis revealed that the relative risk for patient death and graft loss was 3.4 times and 2 times higher for group 1 than for group 2, respectively. An especially low graft survival rate was obtained for donors older than 70 years. Out of 13 recipients receiving grafts from donors older than 70, 5 lost their grafts in the 1st, 4 in the 2nd, 2 in the 3rd post-transplant year. The causes of graft loss are presented in Table 4. The highest graft loss occurred in group 1 during the 1st post-transplant year. That was caused by more frequent acute complications (arterial thrombosis, irreversible acute rejection) in the early post-transplant period but also by more progressive chronic graft failure,

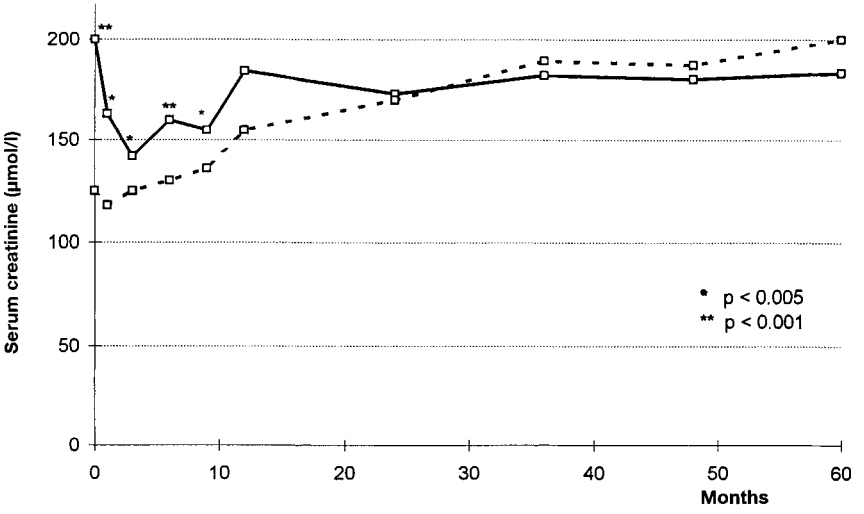

Fig. 1 Post-transplant serum creatinine levels of renal transplant patient receiving grafts from living related donors over 60 years old (—) and younger than 60 years (- - - -). Median values of serum creatinine were compared using the Mann-Whitney U-test and showed a significant difference between the groups during the first 12 months

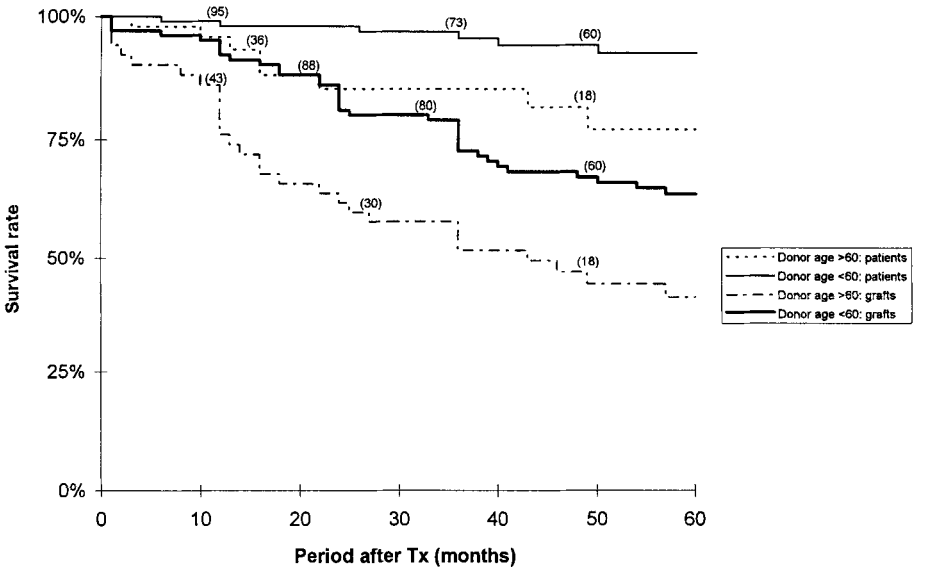

Fig. 2 Patient and graft survival rate as a function of donor age. The numbers in parentheses are the numbers of patients and grafts at risk

due to recurrent glomerulonephritis, and chronic rejection.

In 8 patients from group 1 and in 14 patients from group 2 who developed chronic graft failure, a graft biopsy was performed. Pathohistological analysis revealed similar causes for chronic graft failure in both groups: chronic rejection ($n = 3$ vs 5), cyclosporin-induced chronic nephropathy ($n = 2$ vs 6), and recurrent glomerulonephritis ($n = 3$ vs 3).

Discussion

The lack of available cadaveric kidneys has resulted in an increased number of living related kidney transplantations, including those from older donors. According to the literature, in most countries, 10 %–30 % of all transplanted kidneys have been taken from living related donors [4, 15, 28] or cadaveric donors [22, 24] older than 55 years, but if one scrutinizes donors for normal kidney function, it would appear that even very old donors can be used [3]. In contrast, other authors [11, 16] have reported poor graft survival rates for recipients of old donor kidney grafts, and they do not recommend such transplantations as a standard and safe therapy. The well-known, age-associated, progressive decline in renal function starts after 30 years of age [18], predisposing one to numerous adverse events in the post-transplant period, such as prolonged warm ischemia time during allograft implantation, administration of nephrotoxic drugs, and allograft rejection, all of which contribute to a shortened allograft survival time. These controversial findings have stimulated many studies on the impact of donor age on the outcome of kidney transplantation [4, 6, 15, 28].

Table 4 Causes of patient deaths and graft losses. Data in parentheses indicate patient death or graft loss occurring during the 1st post-transplant year (*CNS* central nervous system, *CGF* chronic graft failure)

	Group 1	Group 2
Number of patients	50	99
Causes of patient deaths:		
Pneumonia	2 (1)	2 (1)
Hepatitis	2 (1)	1
Intestinal bleeding	1	
Pancreatitis		2
CNS insult	1	
Cancer		1
Unknown	2	
Causes of graft loss:		
Arterial thrombosis	1 (1)	
Irreversible acute rejection	2 (2)	
CGF due to surgical complication	3 (2)	
Chronic rejection	3 (1)	4
Chronic cyclosporin nephropathy	2	4 (1)
Recurrent glomerulonephritis	3 (2)	
Unknown	6 (2)	3

In the present study, the outcome of transplantations performed from older living donors (mean age 65 years) was compared to the outcome of transplantations performed from younger donors (mean age 47 years). Except for age, no other significant differences were found between the groups with regard to donor or recipient characteristics. Similar complications appeared during operative and postoperative follow-up in both donor groups. Two of the donors (aged 75 and 58 years) died 2 months after donor nephrectomy, although they had no contraindications for organ donation. Therefore, their deaths could not be related to donor nephrectomy.

Another donor (aged 85), satisfied with the results of the transplantation, did not come in for a check-up until his death 3 years after donor nephrectomy. The medical records of all donors who died after nephrectomy were again carefully examined but revealed no higher donation risk for them than for the other donors.

Like many other authors, we also found a higher incidence of delayed graft function for kidneys obtained from older donors [13, 28]. It could be presumed that the older kidneys, having some degree of morphological [20, 27] or functional lesions, had become more sensitive to immune, ischemic, or toxic influences during the early post-transplant period [13, 26]. Slower improvement in graft function in the early post-transplant period resulted in higher serum creatinine levels in group 1 during the 1st year; thereafter, the serum creatinine levels were equal in both groups until the end of the follow-up period. In contrast to our results and to similar results reported by other authors [13, 28], a recent study has demonstrated reduced graft function with increasing donor and recipient age [12].

An analysis of graft losses revealed a higher incidence of early graft loss in recipients of kidneys from older donors, which is in accordance with previous studies [10, 16, 23]. A higher incidence of chronic graft failure was also noted in group 1. The causes of chronic graft failure confirmed by graft biopsies were chronic rejection, chronic cyclosporin nephrotoxicity, and recurrent glomerulonephritis [6, 10, 23]. In contrast to other authors, almost half of our patients who received kidney grafts from older donors and who developed chronic graft failure lost their grafts during the 1st post-transplant year. It has been proposed that donor age may be involved in the development of chronic rejection [6, 10, 21, 23]. Our analysis showed that chronic graft failure, irrespective of its cause, started earlier and progressed faster in recipients of older kidneys than in recipients of younger kidneys.

The post-transplant course significantly influenced the survival of patients and grafts obtained from older donors, which was worse than for grafts obtained from younger donors.

Recent studies have demonstrated that the sex and age of donors, as well as age differences between donors and recipients, can influence kidney graft outcome. Male donors were found to be better for female recipients, but the cause was unclear [8]. Cadaveric graft survival was better if the donors and recipients were similar in age [5, 7, 11, 22]. Thorogood et al. calculated the relative risk of graft failure [29] and found that both donor age and the age difference between donor and recipient increased the risk for chronic graft failure. Our results obtained for living related donors confirmed these data. The relative risk for patient death and graft loss was higher for patients receiving grafts from older donors.

It may be concluded that kidney grafts from donors older than 60 years may be used for transplantation, but with precautions. Donors older than 70 years should generally be avoided as living kidney donors except in cases where kidney transplantation is the only way to enable patient survival in end-stage renal failure.

References

1. Alexander JW, Vaughn WK (1991) The use of "marginal" donors for organ transplantation: the influence of donor on outcome. Transplantation 51: 135–141
2. Anaise D, Rapaport FT (1993) Use of non heart beating cadaver donors in clinical organ transplantation – logistics, ethics, and legal considerations. Transplant Proc 25: 2153–2155
3. Aswad S, Cicciarelli J, Mendez R, Dessouki M (1992) Renal transplantation from a donor over 60 years old. Transplantation 53: 213–214
4. Campistol JM, Oppenheimer F, Ponz E (1990) Aged kidney donors. EDTA-ERA, Abstract no 198
5. Cecka JM, Terasaki PI (1995) Optimal use for older donor kidneys: older recipients. Transplant Proc 27: 801–802
6. Creagh TA, McLean PA, Donovan MG, Walshe JJ, Murphy DM (1993) Older donors and kidney transplantation. Transpl Int 6: 39–41
7. Donnelly PK, Henderson R (1990) Matching for age in renal transplantation. N Engl J Med 322: 851–852
8. Elgueta S, Fuentes C, Santamaria L, Wegmann ME, Melendez M, and Chilean Renal Transplant Centers (1992) Effects of recipients and donor relationships and sex on graft survival in living-related renal transplantation. Transplant Proc 24: 3074–3075
9. Evans R (1990) Organ donation: facts and figures. Dial Transplant 19: 234–240
10. Geerlings W, Tufveson G, Ehrich JHH, Jones EHP, Landais P, Loirat C, Mallick NP, Margreiter R, Raine AEG, Salmela K, Selwood NH, Valderrabano F (1994) Report on management of renal failure in Europe. Nephrol Dial Transplant 23 [Suppl 1]: 6–25
11. Hardy B, Cicciarelli JC, Iwaki Y, Shaul D, Mendez R (1994) Effect of donor age on graft survival rates in pediatric living-related transplants, first cadaver transplants and regrafts. Transplant Proc 26: 44–45
12. Higgins RM, Sheriff R, Bittar AA, Richardson AJ, Ratcliffe PJ, Gray DWR, Morris PJ (1995) The quality of function of renal allografts is associated with donor age. Transpl Int 8: 221–225
13. Iguro T, Okazaki H, Sato T, Jimbo M, Oguma S (1989) The effect of donor age and sex on cyclosporine associated nephrotoxicity. Transplant Proc 21: 1554–1555
14. Kaplan EL, Meier P (1958) Non parametric estimation from incomplete observations. J Am Stat Assoc 53: 457
15. Kostakis A, Sotirchos G, Stamatiadis D (1990) Outcome of renal transplantation from living related donors (LRD) aged more than 60 years. EDTA-ERA, Abstract no 211

16. Längle F, Sautner T, Grünberger T, Gölzinger P, Schuster G, Pohanka E, Steininger R, Mühlbacher F (1992) Impact of donor age on graft function in living-related kidney transplantation. Transplant Proc 24: 2725–2727
17. Lawless JE (1982) Statistical models and methods for life time data. Wiley, New York
18. Morgan T (1979) Physiologie renale. In: Hamburger J, Crossnier J, Grunfeld JP (eds) Nephrologie, vol 1. Flammarion, Paris, pp 57–98
19. Nathan HM, Jarrell BE, Broznik B (1991) Estimation and characterization of the potential renal organ donor pool in Pennsylvania statewide donors' study. Transplantation 51: 142–149
20. Nyberg G, Hedman L, Blohme I, Svalander C (1992) Morphologic findings in baseline kidney biopsies from living related donors. Transplant Proc 24: 355–356
21. Paul LC (1993) Chronic rejection of organ allografts: magnitude of the problem. Transplant Proc 25: 2024–2025
22. Phillips AO, Bewick M, Snowden SA, Hillis AN, Hendry BM (1993) The influence of recipient and donor age on the outcome of renal transplantation. Clin Nephrol 40: 352–354
23. Raine AEG, Margreiter R, Brunner FP, Ehrich JHH, Geelings W, Landais P, Loirat C, Mallick NP, Selwood NH, Tufveson G, Valderrabano F (1992) Report on management of renal failure in Europe, 1991. Nephrol Dial Transplant 22 [Suppl 2]: 7–35
24. Rosman J, Steinhauslin F, David S, Genton A, Mosimann F, Wauters JP (1992) Impact of recipient and donor age on the outcome of renal transplantation. Transplant Proc 24: 2723–2724
25. Rosner F (1990) Anencephalic infants as organ donors. N Engl J Med 322: 331–332
26. Solez K, Axelen RA, Benediktisson H, Burdick J, Cohen AH, Colvin RB, Croker BP, Droz D, Dunnill MS, Halloran PH, Hayry P, Jannette JC, Keown PA, Markussen N, Mihatsch MJ, Morozumi K, Myers BD, Nast CC, Olsen S, Racusen L, Ramos EL, Rosen S, Sachs DH, Salomon DR, Sanfilippo F, Verani R, Von Willebrand E, Yamaguchi Y (1993) Internal standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 44: 411–422
27. Sugiyama S, Tsuyuki M, Okazaki Y, Takeuchi N, Matsuura O, Ohshima S (1994) Arteriosclerotic lesions of donor kidney and graft survival. Transplant Proc 26: 929–930
28. Sumrani N, Delaney V, Ding Z, Davis R, Daskalakis P, Tejani A, Butt K, Hong J (1991) Renal transplantation from elderly living donors. Transplantation 51: 305–309
29. Thorogood J, Persijn GG, Zantvoort FA, Houwelingen JC van, Rood JJ van (1990) Matching for age in renal transplantation. N Engl J Med 322: 852