

Renal transplantation with donors aged over 50: a long-term, single centre experience

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Summary

Background: Renal transplantation is now considered the best treatment for end-stage renal failure patients. In view of the worldwide growing waiting list, extending donor age is one of the strategies implemented to make more kidneys available for transplantation.

Methods: From October 1983 to February 2000, 324 renal transplantations were performed at Geneva University Hospital, 68 of which were done with kidneys from donors aged over 50 (mean donor age 55.3 + 4.8 years). The following data were analysed at 1, 5 and 10 years and compared between recipients with donors aged over 50 (>50 years) and under 50 (<50 years): actuarial patient and graft survival, serum creatinine, causes of graft loss.

Results: Patient survival at 10 years was 83% with donors <50 years and 61% with donors >50 years (non-significant). Graft survival at 10 years was 61% with donors <50 years and 48% with donors >50 years (non-significant). Graft survival at 10 years or death with functioning graft was 69% with donors <50 years and 68% with donors >50 years (non-significant). Overall, donor age was not a predictive factor for graft survival, as shown by multiple logistic regression.

Conclusions: Kidneys obtained from donors >50 years are suitable for renal transplantation and yield acceptable graft survival.

Keywords: donor age; end-stage renal failure; renal transplantation; retrospective study; haemodialysis; patient survival; graft survival; life expectancy; kidney graft failure

Introduction

Renal transplantation is nowadays widely recognised as the best treatment for patients requiring renal replacement therapies [1]. With an ageing population in dialysis, patients aged over 60 now account for more than 53% of the population on dialysis [2]. Haemodialysis, the most commonly used modality in these patients, is associated with significant morbidity and mortality compared with renal transplantation [1]. As renal transplantation outcomes in older patients have significantly improved [3–5], it is therefore not surprising that the need for donor organs has been steadily rising. Indeed, patients on dialysis are faced with an ever lengthening waiting list for kidney transplantation. In January 2000, 381 patients were waiting for a cadaveric kidney transplant in Switzerland [6].

The growing gap between supply and demand in kidney transplantation calls for the urgent development of strategies to make more kidneys available for transplantation. Such approaches include better detection of potential donors, new

legislation, encouragement of living organ donation, the use of kidneys from non heart-beating donors and the expansion of donor criteria [7–11]. Indeed, the increase in cadaveric renal transplants has been achieved only by the extended use of older donors and donors sustaining non-traumatic death. Furthermore, the welcome decrease in deaths from vehicle accidents has the greatest impact in the 15- to 34-year-old age group, thus decreasing the percentage of young donors available. In parallel, the percentage of donors dying from stroke increased to as much as 42.1% in 1997, according to the 1998 UNOS annual report [12]. Consequently, in the United States the percentage of donors aged over 50 rose from 10.4% in 1988 to 18.4% in 1996 [13]. Advanced donor age is, however, associated with a higher rate of delayed graft function and a poorer long-term graft survival, but results are generally considered acceptable given the limited supply of organs [10, 14, 15]. Practically, this policy has been largely adopted in western countries and it is of importance to accu-

multate transplant results with donors aged over 50. Few data on long-term follow-up of recipients of kidneys obtained from older donors are available. In this retrospective study we report on a single-centre, long-term follow-up of kidney transplantation from donors aged over 50 where age-matching was not a criterion for allocation.

Patients and methods

This retrospective study spans from October 1983, when we started to use cyclosporin routinely, to February 2000. During this period, 324 kidney transplantations were performed in 296 patients. Transplantation procedures were performed in 195 males and 129 females, with a mean age of 46.3 ± 12.8 (SD) years (range 13.3–78.1). Of these, 68 transplants were done with donors over the age of 50 (mean recipient age 48.4 ± 14.7 years; range 13.3–78.1, mean donor age 55.3 ± 4.8 years) and 247 with donors under 50 (mean recipient age 46.1 ± 12.2 years, range 19.1–75.2, mean donor age 29.5 ± 11.7 years). Donor age could not be retrieved in 9 recipients.

Donor suitability was not ascertained differently between the donors <50 years and >50 years and we did not perform pre-transplantation biopsy in the donors >50 years. However, in addition to the absolute contraindications to cadaveric donation, we did not accept organs from donors >50 years with non-oliguric acute tubular necrosis, uncontrolled hypertension or diabetes.

Pre-transplantation screening included cardiac ultrasonography, thallium stress testing, and cerebrovascular and inferior limb doppler studies. Patients were then admitted to the waiting list after correction of any significant vascular and coronary lesions. The main exclusion criteria were positive T-cell lymphocyte cross-match, evidence of active infection, clinically significant cardiac abnormality, malignancy within the previous 5 years and severe psychiatric disorders.

The standard immunosuppression consisted in a cyclosporin-, steroid- and azathioprine-based triple therapy. The Neoral formulation of cyclosporin (Novartis, Basel,

The aims of this study were to determine whether 10-year patient and graft survival could support a policy of cadaveric kidney transplantation with donors aged over 50 in our centre, and what factors played a role in long-term graft and patient survival.

Switzerland) was used as of 1994. Mycophenolate mofetil (Cell-cept, Roche, Basel, Switzerland) replaced azathioprine as of 1996. Thymoglobulins (ATG, Merieux-Pasteur, Marcy l'Etoile, France) and tacrolimus (Prograf, Fusijisawa, Killorglin, Ireland) were used as rescue therapy.

The following data were analysed at 1, 5 and 10 years and compared between recipients of organs obtained from donors aged over 50 (>50 years) and under 50 (<50 years): actuarial patient and graft survival, serum creatinine, causes of graft loss and patient death.

Graft survival of the overall population was analysed according to recipient and donor ages, with cut-off values set respectively at 60 and 50 years, peak % PRA, cold ischaemia time, HLA mismatch, gender, recipient previous nephropathy, and living donor. Selected parameters were assessed as independent factors for graft outcome by multiple regression analysis.

A complete follow-up was obtained for 315 transplantation procedures (97%). Median follow-up was 6.6 years (range 0.2–16 years).

All statistics were performed using the Statistica software package (Statsoft, Tulsa, Oklahoma). Patient and graft survivals were calculated by the Kaplan-Meier method. Survival curves were compared with the Mantel-Cox logrank test. Cox's proportional hazard method was used for multiple regression analysis. Comparison of parametric data was done by Student's *t*-test for continuous variables, and by χ^2 test with Yates' correction or Fisher's exact test, wherever appropriate, for categorical variables. Values of $p < 0.05$ were considered significant.

Results

The statistically significant differences in patient characteristics between both groups were lower HLA mismatch ($p = 0.05$), lower prevalence of chronic glomerulonephritis ($p = 0.04$) and higher prevalence of diabetes ($p = 0.05$) as original nephropathies in the group of recipients of kidneys from older donors (>50 years). The living donor rate was 6% in both groups. Significant differences between the two groups were also found with a shorter cold ischaemia time ($p = 0.024$) and a higher acute rejection rate ($p = 0.02$) for the older donors group. Interestingly, delayed graft function was similar in both groups (21%). Patient characteristics are summarised in Table 1.

Actuarial patient survival at 1, 5 and 10 years was 98, 93 and 61% respectively with donors >50 years and 98, 91 and 83% with donors <50 years ($p = 0.24$; Figure 1A). Actuarial graft survival at 1, 5 and 10 years was 84, 67 and 48% with donors >50

years and 90, 76 and 61% with donors <50 years ($p = 0.18$; Figure 1B). When observations were censored for patient death with functioning graft, actuarial graft survival at 1, 5 and 10 years was 86, 70 and 68% with donors >50 years and 90, 81 and 69% with donors <50 years ($p = 0.33$; Figure 1C).

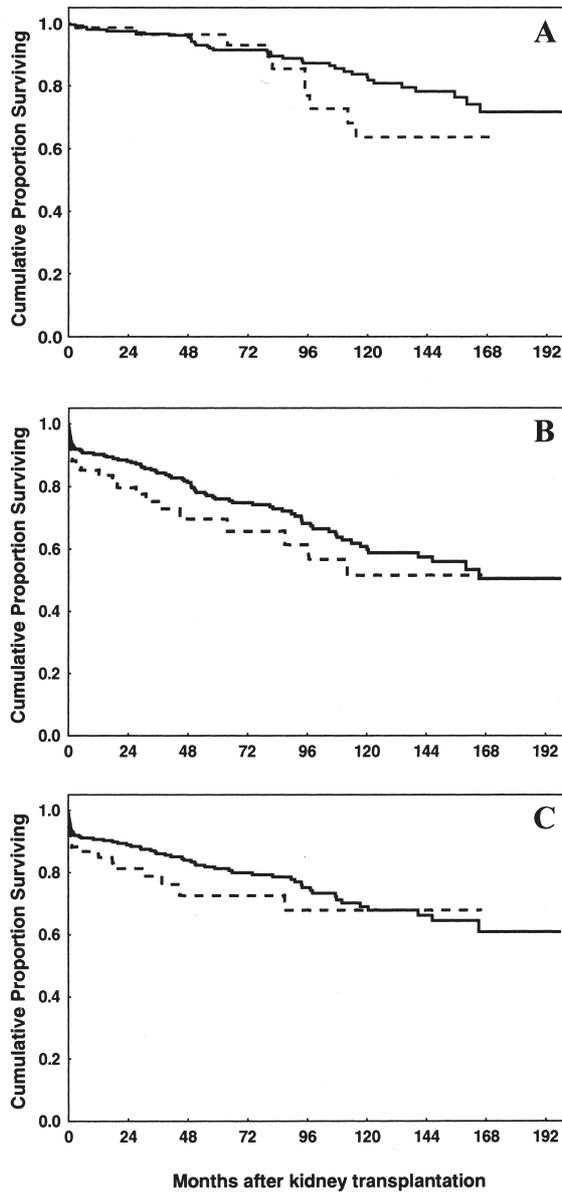
Multivariate analysis of selected variables showed peak PRA, HLA mismatch and acute renal failure to be significant predictive factors for graft survival in this population (Table 2).

Renal function, as assessed by serum creatinine in patients with functioning grafts, was better for recipients of kidneys from younger donors, but differences were significant only at 1 and 10 years follow-up (Table 3).

Causes of graft loss were similar in both groups (Table 4).

Figure 1

Kaplan-Meier analysis of patient and graft survival after kidney transplantation according to age of donor. A, patient survival with donors <50 years (full line, n = 247) and >50 years (dashed line, n = 68); p = 0.24, n.s. (Mantel-Cox logrank test). B, graft survival with donors <50 years (full line, n = 247) and >50 years (dashed line, n = 68); p = 0.18, n.s. C, graft survival censored for patient death with functioning graft with donors <50 years (full line, n = 247) and >50 years (dashed line, n = 68); p = 0.33, n.s.



Discussion

With improving clinical management of the recipient and the progress in immunosuppression, the outcome of transplantation is significantly better than for other renal replacement therapies and is considered the best treatment for end-stage renal disease.

Before the emergence of new techniques in human organ transplantation such as xenotransplantation, expanding the kidney donor pool is the only way to narrow the gap between demand and supply in kidney transplantation. Among various strategies to expand the kidney pool, raising donor age is the easiest to implement and thus the most commonly used [12].

The major concern with kidneys from older donors is their diminished half-life as compared to those from younger donors. At 1 and 2 years post-transplantation, graft survival with donors aged over 56 is decreased by 10 and 14% respectively, as compared to donors aged between 16 and 45 [10]. Using the same registry (UNOS), it has been estimated that donor age is accountable for 21% of graft loss at 5 years post-transplantation [1] and is a predictive factor for graft loss with a relative risk between 1.4 and 2.5 (145-17). Some authors have nonetheless reported good graft survival when kidneys from older donors are transplanted into older recipients, and have advocated donor-recipient age matching [18]. By contrast, a recent publication reported a 14% decrease in 5-year graft survival for patients over 60 who are transplanted with kidneys from donors over 60, as compared to kidneys from donors under 60 [19], a finding which does not speak in favour of an age-matching policy.

Given the relatively small size of our centre and of our network for organ sharing (Swisstransplant), age-matching was not a priority for our patients, as illustrated by the almost identical recipients' mean age in both groups.

Graft and patient survivals at 1, 5 and 10 years were slightly better in the group transplanted with kidneys harvested from younger donors, but the differences observed are not significant. This observation is supported by the fact that donor age was not a predictive factor of graft survival in multiple logistic regression analysis. Though we cannot exclude a type II error on account of our relatively small number of patients, the similar survival in both groups might be explained by other factors. Firstly, a shorter cold ischaemia time (17.3 ± 7.3 hr vs. 19.5 ± 6.4 hr) in the group with older donors may play a role if we assume that older organs have less viable nephrons. The shorter cold ischaemia time in the group of donors >50 years is explained by the predominance of local donors. Although 2 hours may appear clinically irrelevant, it has recently been shown that a relatively short prolonging of cold ischaemia time for the kidney transplanted second in kidney pairs may result in increased acute tubular necrosis, as demonstrated on a renogram [20]. The

Table 1

Patient characteristics.

	Donors >50 years (n = 68)	Donors <50 years (n = 247)	p
Donor age (yr)	55.3 ± 4.8	29.5 ± 11.7	
Recipient age (yr)	48.4 ± 14.7	46.1 ± 12.2	n.s.
Recipients >60 yr (%)	22	14	n.s.
Male/female ratio	71/29	57/43	n.s.
Diabetes (%)	22	12	0.05
Hypertension (%)	18	12	n.s.
Chronic GN (%)	18	32	0.04
PCKD (%)	25	17	n.s.
Others (%)	16	27	n.s.
Retransplant (%)	9	18	n.s.
Cadaveric donor (%)	94	94	n.s.
Living donor (%)	6	6	n.s.
Max PRA >40% (%)	11	14	n.s.
HLA mismatch (1-6)	3.3 ± 1.3	3.6 ± 1.2	0.05
Cold ischaemia time (hr)	17.3 ± 7.3	19.5 ± 6.4	0.024
Delayed graft function (%)	21	21	n.s.
Acute rejection episodes (%)	55	37	0.02
Half-life of kidney grafts (mo)		126	171

similar rate of delayed graft function in both groups of our study suggests that kidneys of older donors are more susceptible to cold ischaemia. Secondly, the majority of our older donors were under the age of 60 (mean 55.3 ± 4.8 years), which assigns them to the category of "young old donors" since one-year results are now being published with kidneys from donors between the ages of 60 and 74 years [11]. In addition, recently published Japanese data on living donor kidney transplantation report that graft survival at 10 years remains at around 70% with donors aged 50 to 59, but declines dramatically to 45% with donors over 60 [21]. Finally, more careful selection of donors aged over 50 may have reduced co-morbidity in those donors.

We observed a high rate of acute rejection episodes with donors aged over 50, despite a similar incidence of delayed graft function and better HLA matching. We were unable to account for this on the basis of the variables analysed, and it suggests that older kidneys are more susceptible to acute rejection which may reflect increased renal damage during ischaemia time.

Measured serum creatinine at 1 and 10 years in patients with functioning grafts indicates slightly diminished renal function. This result is

probably explained by the nephronic insufficiency induced by senescence, as previously reported [14], although we should be cautious about the statistical significance at 10-year follow-up, given the small number of patients at risk at this time point. There was also a statistical trend towards higher mortality at 10-year follow-up in recipients with donors aged over 50. A confounding bias may be the higher percentage of diabetics in this group.

Kidney grafts from donors >50 years offer, despite a shorter estimated half-life (126 months as compared to 171 months with donors <50 years), acceptable long-term survival, as illustrated by our results in a non age-matching transplantation programme. Shortening cold ischaemia time is an important goal to be considered when using these donors. In addition, with the availability of new kidney-sparing immunosuppressive drugs such as sirolimus and mycophenolate mofetil, tailored immunosuppression may further improve the half-life of kidney grafts from old donors. Our data suggest that cadaveric kidneys from donors aged up to 60 years should be transplanted. Kidneys from donors aged over 60 can also be transplanted, provided the age is matched with recipient age and sufficient renal integrity has been demonstrated *either by the patient's history and renal results* or on pre-transplant biopsy [22]. As the first identification of a potential donor is frequently done by internists, emergency and ICU staff, it is of importance to emphasise that age is not a contraindication for selection of a potential kidney donor.

In summary, given the poor survival and quality of life of patients on haemodialysis and the increasing demand for transplantation, especially in patients over 60 [23], our data indicate that organ procurement in donors over 50 should always be considered, particularly when the donors are local with an anticipated short cold ischaemia time. On account of the foreseeable shorter life expectancy of end-stage renal failure patients above the age of 60, a strategy based on the allocation of older kidneys to older donors should be further studied.

Table 2
Predictive factors of graft survival.

Factor	p value	
Recipient age*	0.46	n.s.
Donor age*	0.28	n.s.
Peak%PRA*	0.05	
Cold ischaemia time*	0.56	n.s.
HLA mismatches*	0.02	
Acute rejection**	0.001	
Gender**	0.67	n.s.
Nephropathy**	0.53	n.s.
Living donor**	0.63	n.s.

* Cox's proportional hazard method

** Mantel-Cox logrank test

Table 3
Serum creatinine level by donor age in kidney recipients.

Follow-up	>50 years (n)	S-creat. (mmol/l)	<50 years (n)	S-creat. (mmol/l)	p
1 year	43	166 ± 54	205	129 ± 40	<0.0001
5 years	18	153 ± 41	125	135 ± 51	n.s.
10 years	7	189 ± 41	52	122 ± 62	0.02

Table 4
Causes of graft loss by donor age in kidney recipients.

Etiology	>50 years (n = 68)		<50 years (n = 247)		p
	n	%	n	%	
Death with functioning graft	5	24	18	23	n.s.
Acute rejections	6	29	17	22	n.s.
Chronic rejections	6	29	33	42	n.s.
Technical complications	4	19	5	6	n.s.
Recurrence	0	0	3	4	n.s.
Others	0	0	2	3	n.s.

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References

- 1 Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725-30.
- 2 Cecka JM, Terasaki PL. The UNOS scientific Renal Transplant Registry. In: Terasaki PL, Cecka JM, eds. *Clinical Transplants*. Los Angeles: UCLA Press; 1993.
- 3 Tesi RJ, Elkhamamas EA, Davies EA, Henry ML, Ferguson RM. Renal transplantation in older people. *Lancet* 1994;343:461-4.
- 4 Cantarovich D, Baatrad R, Baranger T, Tirouvanziam A, Le Sant JN, Hourmant M, et al. Cadaveric renal transplantation after 60 years of age: a single center experience. *Transplant Int* 1994;7:33-8.
- 5 Saudan P, Berney T, Leski M, Morel P, Bolle JF, Martin PY. Renal transplantation in the elderly: a long term, single center experience. *Nephrol Dial Transplant* (in press).
- 6 Rapport d'activités 1999, Laboratoire national de référence pour l'histocompatibilité, Hôpital cantonal universitaire de Genève, Suisse.
- 7 Cho YW, Terasaki PI, Cecka JM, Gjertson CW. Transplantation of kidneys from donors whose hearts have stopped beating. *N Engl J Med* 1998;338:221-5.
- 8 Berney T, Malaise J, Mourad M, Morel P, Squifflet JP. Laparoscopic and open live donor nephrectomy: a cost/benefit study. *Transpl Int* 2000;13:35-40.
- 9 Gjertson DW, Cecka JM. Living unrelated donor kidney transplantation. *Kidney Int* 2000;58:491-9.
- 10 Alexander JW, Bennett LE, Breen TJ. Effect of donor age on outcome of kidney transplantation. *Transplantation* 1994;57:871-6.
- 11 Andres A, Morales JN, Herrero JC, et al. Double versus single renal allografts from aged donors. *Transplantation* 2000;69:2060-6.
- 12 1998 Annual Report. US Scientific registry of transplant recipient and the organ procurement and transplantation network. Transplant data 1988-1997. Richmond, U.S. Department of Health and Human Services, Office of special programs, Division of transplantation UNOS.
- 13 Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000;342:605-12.
- 14 Terasaki PL, Gjertson DW, Cecka JM, Takemoto S, Cho YW. Significance of the donor age effect on kidney transplants. *Clin Transpl* 1997;11:366-72.
- 15 Moreso F, Seron D, Gil-Vernet S, Riera L, Fulladosa X, Ramos R, et al. Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients. *Nephrol Dial Transplant* 1999;14:930-5.
- 16 Morris PJ, Johnson RJ, Fuggle SV, Belger MA, Briggs JD. Analysis of factors that affect outcome of primary cadaveric renal transplantation in the UK. *Lancet* 1999;354:1147-52.
- 17 Matas AJ, Gillingham KJ, Humar A, Dunn DL, Sutherland DER, Najarian JS. Immunologic and nonimmunologic factors: different risks for cadaver and living donor transplantation. *Transplantation* 2000;69:54-8.
- 18 Cecka JM, Terasaki PL. Optimal use for older donors kidneys: older recipients. *Transplant Proc* 1995;27:801-2.
- 19 Basar H, Soran A, Shapiro R, Vivas C, Scantlebury VP, Jordan ML, et al. Renal transplantation in recipients over the age of 60: the impact of donor age. *Transplantation* 1999;67:1191-3.
- 20 Tandon V, Botha JF, Banks J, Pontin AR, Pascoe MD, Kahn D. A tale of two kidneys - how long can a kidney transplant wait? *Clin Transpl* 2000;14:189-92.
- 21 Shimmura H, Tanabe K, Ishikawa N, Kanematsu A, Tokumoto T, Oshima T, et al. Influence of donor renal reserve on the long-term results of living kidney transplantation from elderly donors. *Transplant Proc* 1999;31:2874-6.
- 22 Kumar MS, Panigrahi D, Dezii CM, Abouna GM, Chvela R, Brezin J, et al. Long-term function and survival of elderly donor kidneys transplanted into young adults. *Transplantation* 1998;65:282-85.
- 23 Ponticelli C. Should renal transplantation be offered to older patients? *Nephrol Dial Transplant* 2000;15:315-7.

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