Living Donor Transplantation: Long-Term Evolution Related to Age Matching

E.A. Florit[a], F. Diekmann[a,*], K. Budde[b], P. Glander[b], L. Liefeldt[b], J. Nistal[a], F. Oppenheimer[a], J.M. Campistol[a], and S. Brakemeier[b]

[a]Servicio de Nefrología - Clinical Institute of Nephrology and Urology, Hospital Clinic, Barcelona, Spain; and [b]Nephrologie, Charité Campus Mitte, Berlin, Germany

ABSTRACT

The lack of donors is favoring living kidney donor (LKD) transplantation worldwide, quite often beyond the classic age-matching rules. We analysed renal function (RF) at 1 and 5 years in all donor and recipients as well as death-censored graft and patient survival. LKD recipients were divided into 4 subgroups: young recipients-young donors (YR-YD; N = 355), elderly recipients-young donors (ER-YD; N = 13), young recipients-elderly donors (YR-ED; N = 67), and elderly recipients-elderly donors (ER-ED; N = 38). "Elderly" was defined as ≥60 years. RF was better in those who received a young allograft (YR-YD/ER-YD) at any time ($P < .001$). There was a trend toward higher proteinuria among the recipients of an old allograft (YR-ED/ER-ED) at any time (P = not significant [NS]). However, our population showed low levels of proteinuria and this was not a risk factor for graft failure. Logistic regression model showed that creatinine level at 1 year is a good predictor of graft losses. Graft survival was worse in the allografts from elderly donors ($P < .001$). Analysing the young recipients, renal survival was inferior in those who received an old kidney (YR-ED; $P < .00005$) as well as mortality rates at 14 years ($P = .03$). The RF of young (N = 295) and elderly donors (N = 98) was optimal with no progression to ESRD or deaths registered during follow-up. In conclusion, young recipients of elderly kidneys pay the price of a worse RF, allograft prognosis, and patient prognosis. The pair YR-ED is a doable option, but we recommend age matching when it is possible.

END-STAGE RENAL DISEASE (ESRD) is an increasing problem worldwide. Kidney transplantation is the best treatment in terms of patient survival, quality of life, and long-term costs. In contrast, the waiting lists are becoming longer, which is making the matching criteria more flexible with time. Among different options, living kidney donation (LKD) appears to have the best clinical outcomes and is another good source of allografts. In this scenario, greater flexibility is especially reflected in age matching transgressing the classical rule of "old-for-old" and "young-for-young." Our aim was to study the renal function (RF), allograft survival, and patient survival of living donors and recipients in 2 European centers.

METHODS

We retrospectively studied living kidney donors and recipients from 2 hospitals: Charité Campus Mitte (Berlin) and Hospital Clinic (Barcelona).

All cases included were adults. Variables were collected at 1 and 5 years after transplantation.

The cut-off age to create comparative groups was set arbitrarily at 60 years.

Initially, 4 cohorts were created according to age at time of transplantation: young recipients (YR), young donors (YD), elderly recipients (ER), and elderly donors (ED). To make a deeper analysis, 4 subgroups were created among the recipients again depending on the age at transplantation: (1) young recipients-young donors (YR-YD); (2) elderly recipients-young donors (ER-YD); (3) young recipients-elderly donors (YR-ED); and (4) elderly recipients-elderly donors (ER-ED). Normal variables were expressed as mean ± standard deviation and t test was performed as an inference method. Asymmetric variables were expressed as median with its interquartile range and

*Address correspondence to Fritz Diekmann, Clinical Institute of Nephrology and Urology, Hospital Clinic, Calle Villarroel, 170, Barcelona, Spain 08036. E-mail: fdiekman@clinic.ub.es

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Table 1. Four Main Group Characteristics

Variable	YR	YD	ER	ED	*P*
Sample size (N)	408	295	65	98	
Age (y)	38 ± 11	45 ± 8	64 ± 4	65 ± 4	<.05
Gender	M = 62%	M = 38%	M = 65%	M = 28%	<.05
	F = 37%	F = 62%	F = 35%	F = 72%	
Proteinuria/24 h (1 y)	157 (110–239)	107 (76–141)	215 (129–404)	101 (78–129)	<.05
Proteinuria/24 h (5 y)	157 (98–352)	95 (72–128)	180 (90–548)	105 (78–137)	<.05
Systolic BP (1 y)	121 ± 34	126 ± 12	120 ± 43	127 ± 27	NS
Systolic BP (5 y)	123 ± 23	122 ± 14	141 ± 18	122 ± 10	<.05
Diastolic BP (1 y)	71 ± 21	76 ± 9	63 ± 23	72 ± 15	NS
Diastolic BP (5 y)	75 ± 14	77 ± 10	72 ± 7	71 ± 7	NS
CMV (IgG positive)	28.9%	21.7%	38.5%	25%	<.05
HCV (antibodies)	5.1%	0%	6.2%	0%	-

Abbreviations: M, male; F, female; BP, blood pressure; NS, not significant; CMV, cytomegalovirus; Ig, immunoglobulin; HCV, hepatitis C virus.

nonparametric tests (Kruskal-Wallis, Mann-Whitney, and Wilcoxon) were used. Nominal data were analyzed using the chi-square test. Survival analysis was performed in the 4 groups of recipients using Kaplan-Meier estimates. Death-censored allograft survival was recorded at 5 years. The statistical method used to establish differences in survivals rates was the log-rank test. Statistical difference was set at <.05. Multivariate analysis using multiple regression was conducted to determine which variables were related to the main events in our study: graft losses and patient deaths. Confidence interval was set at 95%.

RESULTS

A total of 866 patients were included. Demographic and main characteristics are depicted in Tables 1 and 2.

As shown in Table 2, cytomegalovirus (CMV) were more prevalent in the ER-YD, whereas positive hepatitis C virus serology (HCV) was more frequent in the ER-ED subgroup.

RF

In Fig 1, serum creatinine and Modification of Diet in Renal Disease-4 (MDRD-4) are shown. RF significantly improved at 5 years in the donors. However, the recipients had worse RF at 5 years with significance only in the young recipients ($P < .0001$).

When it comes to the recipient subgroup analysis, RF was better in those who received a young allograft (YR-YD/ER-YD) at any time ($P < .001$).

Proteinuria

Proteinuria was higher in recipients than in donors at any time point (Table 1), without significant intragroup changes over time (P = not significant [NS]).

Recipients of an old allograft (YR-ED/ER-ED) had higher levels of proteinuria at 5 years (Table 2).

Analyzing the evolution of proteinuria with time, the YR-ED cohort was the only group that showed a trend to increase at 5 years whereas the rest tended to decrease (P = NS).

In general, proteinuria was low and could not be identified as a risk factor for graft loss in our patient cohort.

Table 2. Main Characteristic of the Recipient Subgroups

Variable	YR-YD	ER-YD	YR-ED	ER-ED	*P*
Sample size (N)	355	13	67	38	
Age (y)	38 ± 12	63 ± 3	40 ± 9	65 ± 4	.0001
Gender	H = 61%	H = 62%	H = 58%	H = 68%	.05
	M = 39%	M = 38%	M = 42%	M = 32%	
Proteinuria/24 h (1 y)	160 (108–269)	176 (108–370)	198 (139–524)	242 (118–344)	NS
Proteinuria/24 h (5 y)	155 (95–355)	112 (58–667)	240 (142–444)	186 (133–645)	.049
Diabetes (1 y)	2.8%	7.7%	7.5%	10.5%	
Diabetes (5 y)	2.5%	7.7%	7.5%	10.5%	
Systolic BP (1 y)	119 ± 33	125 ± 43	126 ± 38	116 ± 45	.0001
Systolic BP (5 y)	123 ± 21	138 ± 19	123 ± 29	143 ± 17	.0001
Diastolic BP (1 y)	70 ± 20	67 ± 23	73 ± 22	60 ± 23	.0001
Diastolic BP (5 y)	75 ± 14	75 ± 9	74 ± 18	70 ± 5.8	.0001
CMV	27.3%	84.6%	31.3%	36.8%	.002
HCV	4.8%	0%	6%	10.5%	-
Time on dialysis (d)	898 (304–2952)	1129 (541–1842)	1119 (403–2181)	750 (412–1422)	NS
Cold ischemia (min)	55 (45–60)	52 (41–71)	45 (38–71)	50 (40–69)	NS
Warm ischemia (min)	128 (2–249)	4 (1–219)	2 (1–180)	127 (3–186)	NS
DGF	6/157 (3.8%)	1/13 (7.7%)	3/31 (10.7%)	0/19 (0%)	-

Abbreviation: DGF, delayed graft function.

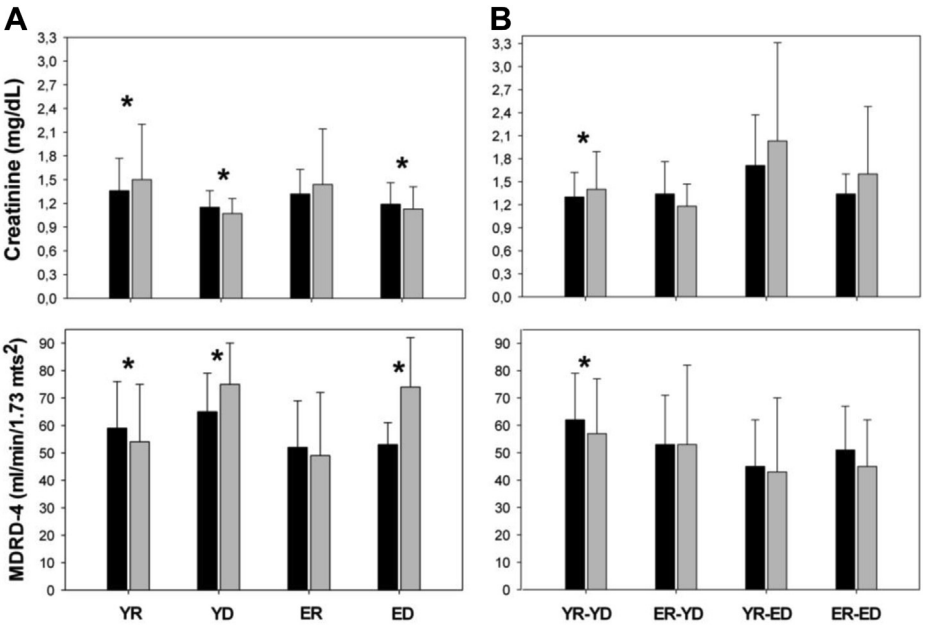

Fig 1. Panel **A** shows RF in the whole population studied. Panel **B** shows RF in the recipients organized in subgroups. Black bars indicate mean values at 1 year and grey bars at 5 years. Lines marks +1 SD. *Statically different.

Allograft and Patient Survival

At 5 years (Fig 2), death-censored graft survival was worse in the allografts from elderly donors ($P < .001$). In contrast, among the patients who received a young kidney, the YR-YD subgroup showed 3.3% of graft loss whereas the old recipients lost none.

As expected, elderly recipients had worse survival rates (Fig 2). This is more evident in the ER-YD subgroup, accounting for a cumulative survival rate of 76.9% versus 86.8% in the ER-ED at 14 years (P = NS). In contrast with this negative trend in mortality, the ER-YD group showed no graft loss.

Assessing outcomes in young recipients, the subgroup YR-ED had more fatal events ($P = .03$) and a higher incidence of graft loss at 5 years ($P < .0005$) in comparison with the YR-YD subgroup.

Conversely, there were no fatal events or kidney losses among the donors.

Multivariate Analysis

The logistic regression model for graft loss included the following: creatinine, systolic blood pressure (BP), diastolic BP, and proteinuria (4 categories were created using as cutoff points 1 standard deviation). Creatinine was the only good predictor (odds ratio [OR], 11.9; confidence interval [CI], 3.8–37; $P = .0001$). In the subgroup analysis, creatinine was significant only in the YR-YD cohort (OR, 6.7; CI, 1.1–39; $P = .033$). It is worth it to mention that proteinuria

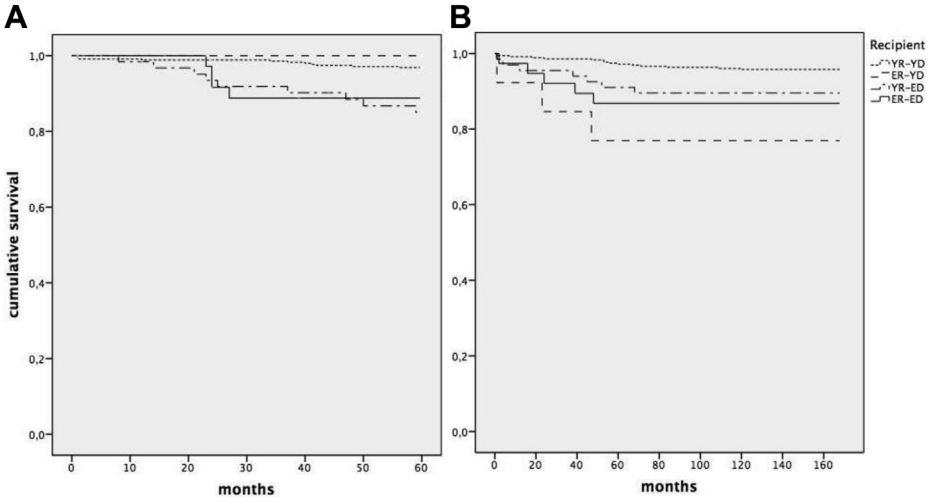

Fig 2. Allograft and recipient survivial. (**A**) Kaplan-Meier survival of death-censored allograft. (**B**) Survival of recipients at 14 years.

behaves as a confusing variable, but it was not excluded from the model because it is clinically relevant. The variables included in the model for fatal events were creatinine, time on dialysis, systolic BP, diastolic BP, and diabetes. We could not demonstrate any statistical relationship between variables and death.

Both models used variables measured at 1 year after transplantation and were chosen based on clinical experience.

DISCUSSION

Due to donor scarcity, alternative sources have been exploited. Therefore, over the last few years persons of advanced age have increasingly been accepted for LKD.

There are plenty of publications engaging big populations that showed better outcomes in elderly LKD than in deceased donor kidneys (even with poor HLA matching). However, it is also clear that younger allografts had superior results than the formerly mentioned options [1–4].

The influence of age on allograft outcomes from deceased donors was addressed in many studies with controversial results. On one hand, most authors could not detect a change in short-term graft survival (within 3 years of observation) when the difference of age between donor and recipient was >5 years in comparison with less age variation [5–7]. Furthermore, Alexander et al showed in >30,000 patients that donor and recipient age were independent risk factors for graft failure [8].

On the other hand, a negative effect on graft survival was reported (in a less powered study) if the difference of age was more than 5 years [9].

Age matching was also studied by Waiser et al in 1269 cadaveric donors transplants, recommending to avoid the implantation of old kidneys in young patients (cutoff age, 55 years old). They observed worse graft survival at 8 years in this group when it was compared with young recipients with young allografts [10]. These results were similar to those of Cecka and Terasaki [11].

Remarkably, those diverse conclusions in the cited references can be explained by the different criteria used to define graft survival (death-censored kidney failure or death with functioning graft) or the observation periods.

Net balance seems to indicate that age matching is a good practice when dealing with a deceased donor and even an easy decision with the actual long waiting lists. But, in the case of LKD, this is more difficult because it is quite common to find big difference in ages between the patient and her/his possible candidates.

Controversy about age matching continues in the LKD scenario. Some studies found that graft loss was not associated with aged donors (older than 60 years of age) [12]. However, when the donor cut-off age was set at ≥70 years Berger et al found worse survival in those aged grafts and comparable with allografts from deceased standard criteria donors [2]. In addition, a large Canadian review with 49,589 patients showed a double risk of graft failure when old donors (>60 years old) donate their kidneys to younger patients [14].

In our study, these observations were consistent. Interestingly the subgroup YR-ED showed the higher rates of death-censored graft losses. What is more, the mortality rates at 14 years were particularly high in comparison with the rest of the young recipients. Nevertheless, it is important to remark that this group had an increased rate of delayed graft function (DGF).

It was previously hypothesized that this phenomenon is due to increased rates of acute and chronic rejection from young (more reactive) immunologic systems over old (more sensitive to stress) kidneys [5,10,13–15]. We did not assess that effect in our study, but we agree with that hypothesis.

More studies are needed to achieve stronger evidence, but, according to cited publications and our result, the decision to provide an old kidney transplant for a young patient is something to apprise very meticulously. The benefits are to reduce the waiting time to get a kidney from a deceased donor with possible implications on economics and cardiovascular risk. A feasible solution can be to encourage an exchange transplantation program matching the age [3,13].

In previous publications, proteinuria was associated with reduced graft survival regardless of living or deceased donation. This negative effect was especially evident with high-grade protein loss (>1500 mg/d) [16–18]. In our cohort of recipients, proteinuria levels were quite low. Interestingly, YR-ED showed a trend to increase proteinuria between 1 and 5 years, and at the same time it was the subgroup with the poorest outcomes (without reaching statistical significance). Nevertheless, in our logistic regression model urine protein levels were not a good indicator for graft losses. In contrast, creatinine level measured at 1 year was significantly related to graft outcomes at 5 years (especially in young patients with young allografts). Despite the fact that we could not find significance in proteinuria, we still support the assessment of this clinical parameter as an unspecific general indicator of graft health.

Last, we want to point out that donor kidney function remained stable over time regardless of age. These findings strengthen the evidence that kidney donation is safe.

In conclusion, RF, proteinuria, and graft survival are better in patients who receive young kidneys regardless of the age of the recipient. In our study we observed differences in renal and patient outcomes according to donor age in young recipients. This should be considered at the time of donor evaluation, especially when several donors are available.

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