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Original Article

Kidney Transplantation from Living-Unrelated and Elderly Living-Related Donors: Analysis of 5 Years Graft Survival and Outcome

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Abstract

Introduction. The shortage of kidney availability has increased utilization of other donor categories. The aim of our study was to compare the graft survival and outcome between living-unrelated donors (LURD) and elderly living related donors (LRD).
Methods. Fifteen LURD kidney transplanted patients in the period between 2000 and 2006, and 18 randomly selected recipients from elderly LRD (>60 years) kidneys were retrospectively evaluated from their patients' charts. The regular immunosuppressive protocol consisted of induction therapy with steroids and IL-2 receptor antibodies (Daclizumab in five doses), and maintenance therapy with mofetil mycophenolate, cyclosporine A and steroids. The analyzed variables were recipient and donor age and sex, glomerular filtration rate of donated kidney (evaluated by DTPA scan of the donor), HLA matching, cold ischemic time (CIT), delayed graft function (DGF), acute rejection episodes (AR), urinary infections (UTI), present status of the graft (determined by estimated GFR), and graft survival data.
Results. The two groups were similar with regard to age, gender and body weight of the recipients, CIT and cyclosporine targeted C_0/C_2 levels. The LURD group donors were younger, and GFR of the donated kidney signifycantly higher when compared to the elderly LRD group, (47,6±11.4 vs. 65,9±3,6 years, p<0,05; 53,3±14,2 vs. 44,1 ±10,1 ml/min; p<0,05). LURD group of patients was characterized by significantly higher percentage of AR and UTI, as well as longer hemodialysis duration when compared to the elderly LRD group (34,5% vs. 18,6%, p<0,05; and 36,4% vs. 20,2%, p<0,05; 34,7±12,2 vs. 8,0±6,9 months, p<0,01). No difference in graft survival rates was found between the groups at 5 years follow up, with graft survival rate of 100% in both groups. In addition, the graft function at 5 years after transplantation did not differ significantly between the groups, although the LURD group maintained slightly higher GFR compared to the elderly LRD group (55,7±15,6 vs. 46,3±16,8 ml/min, p>0.05).
Conclusions. Kidney transplant recipients from LURD have shown to yield 5 years graft survival rates and outcome similar to that of LRD older than 60 years. A possible partial explanation may be the higher GFR of donated kidney in LURD group, compared to the lower number of HLA mismatches in the group of kidney transplants from older LRD and their lower percentage of UTI and episodes of AR. Although these results are obtained in a pilot study, they confirm that in the presence of organ shortage from cadavers, LURD and older LRD may become a valuable source of potential organ for patients on the kidney waiting list.

Key words: kidney transplantation, living kidney donation, elderly related donors, unrelated donors

Introduction

Kidney transplantation with organs from living related donation (LRD) has been performed for many years with good results [1]. Namely, since its introduction over 50 years ago, live-donor kidney transplantation has been associated with better graft and patient outcomes compared to the deceased donor kidney transplantation [2,3].
However, organ shortage and a steadily increasing waiting time for cadaver kidney transplant have made it necessary to search for alternatives. Kidney transplantation from living unrelated donors (LURD), i.e. between persons who have close emotional bonds only, has been proposed as another possibility. Thus, the evidence of unexpectedly high rates of survival of kidney grafts from spouses and other living unrelated donors in patients with end-stage renal disease has been mounting in recent years [4-7]. Moreover, donors aged >60 years are now frequently accepted as another alternative for living kidney transplantation [8-10].
The aim of our study was to identify and evaluate the risk factors for graft outcome and survival and their comparison between the LURD and elderly LRD (>60years) groups of patients.

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Materials and methods

In our study 15 kidney transplant patients from LURD performed in the period 2000-2006, and 18 randomly selected recipients from elderly LRD (>60 years) were retrospectively evaluated from their patients' charts. All kidney transplant recipients included in the study received their first allograft. As an induction therapy we used methylprednisolone (500mg) and IL-2 receptor antibodies-Daclizumab (Zenapax®; 1mg/kg/BW at implantation and thereafter every 2 weeks in five doses). The maintenance immunosuppression consisted of cyclosporine A (Neoral®; 4-6mg/kg/day) initiated at least 36hrs after transplantation to reach target C2 levels of 800-1200 ng/ml, prednisolone (1 mg/kg/day tapered to 0,1 mg/kg/day after 4 weeks) and mycophenolate mofetil (Cellcept®; 1 g bid.).

Patients with DGF during the first postoperative month, manifested as post-transplant acute tubular necrosis (ATN), were treated with hemodialysis, and those who experienced an episode of acute rejection AR (increase in serum creatinine >20% or a decrease in urine output for 2 consecutive days), were treated with pulse corticosteroids. Biopsies were done by ultrasound-guided automated gun. Biopsy specimens were considered as adequate if they contained more than 7 glomeruli and at least one artery that were further histologically processed according to the Banff 97 scoring scheme [11].

The analyzed variables were as follows: recipient and donor age and sex, glomerular filtration rate of donated kidney (evaluated by DTPA scan of the donor), HLA matching, cold ischemic time (CIT), delayed graft function (DGF), acute rejection episodes (AR), number of urinary tract infections (UTI), present status of the graft (determined by estimated GFR e.g. calculated creatinine clearance-cClCr), and graft survival data. There were two groups of patients: Group 1: LURD group (n=15), including 10 kidneys donated from female and 5 from male spouses, and Group 2: LRD (>60 yr) group (n=18) consisted of 4 siblings, 13 parents and one cousin.

The clinical and biochemical data were recorded at the time of transplantation, at 1th, 6 months, and at 1th and 5 years posttransplant.

Data are expressed as mean values ± SD for continuous variables and as percentage for categorical data. For numeric data, ANOVA and Student's *t* test to compare the differences between 2 groups and Kruskal-Wallis and Mann-Whitney *U* test as nonparametric analysis were used when appropriate. Chi square (Fisher's exact test) was used to compare the categorical data. A difference was considered significant at a *P* value of <0.05.

Results

The groups did not differ regarding the cause of ESRD (Table 1).

Table 1. Demographic characteristics of recipients (cause of ESRD)

	LURD (n°=15)	LRD>60 yr (n°=18)
Glomerulonephritis	7	9
Diabetes	2	3
Hypertensive renal disease	2	2
Polycystic renal disease	1	1
Reflux nephropathy	0	1
Lupus nephropathy	0	1
Other	3 pts	2 pts

Table 2. Comparison of demographic characteristics, biochemical and clinical data between the groups

Parameters	LURD (n°=15) Mean±SD	LRD>60yr (n°=18) Mean±SD	p-value
Donor age (yr)	47,6±10,4	65,9±3,6	<0,05
Recipient age (yr)	35,1±9,8	30,3±10,0	ns
Recipient BMI	22,4±4,0	22,8±3,8	ns
GFR don. kidney	53,3±14,2	44,1±10,1	<0,05
Time on HD (mo)	34,7±12,2	8,0±6,9	<0,01
HLA mismatch	4,4±1,8	2,1±1,1	<0,01
CIT (hours)	2,5±1,4	3,1±1,8	ns
DGF	15,3%	17,6%	ns
AR post-transplant	34,5%	18,6%	<0,05
UTI post-transplant	36,4%	20,2%	<0,05
CyA (C2 level)	867,4±28,8	748.6±36,6	ns
CAN evidence	21,4%	39,5%	<0,05
Graft survival 5yrs rate	100%	100%	ns

Baseline patients' characteristics are shown in Table 2.

The groups were similar with regard to recipient's age, gender and body weight and cyclosporine targeted C_2 levels. LURD recipients tended to be older (35.1±9.8 vs. 30,3±10,0 years), and had significantly higher HLA mismatching (4,4±1,8 vs. 2,1±1,1, p<0.01). On the other hand, CIT in the group of LRD recipients seemed to be longer (3,1±1,8 vs. 2,6±1,4 hours), and the percentage of DGF in this group higher 17,6% vs. 15,3%, but none of these variables have reached the level of significance, when compared to the LURD group.

Nevertheless, donors in the LURD group were younger, and GFR of donated kidney was significantly higher than those in the elderly LRD group (47,6±11,4 vs. 65,9±3,6 years, p<0,05; 53,3±14,2 vs. 44,1±10,1 ml/min; p<0,05). In addition, LURD group of patients was characterized by significantly hig-

her percentage of AR and UTI, as well as longer hemodialysis duration when compared to the elderly LRD group (34,5% vs. 18,6%, p<0,05; and 36,4% vs. 20,2%, p<0,05; 34,7±12,2 vs. 8,0±6,9 months, p<0,01) (Table 2).
Importantly, chronic allograft nephropathy (CAN) histological evidence was present in a significantly higher percentage in biopsy specimens of the elderly LRD group of patients when compared to those of LURD group (39,5% vs. 21,4%, p<0,05). No difference in graft survival rates was found between the groups at 5 years follow up, with graft survival rate of 100% in both groups.
Serum creatinine levels (sCr) were slightly higher while estimated GFR (calculated creatinine clearance-cClCr) tended to be lower during the whole period of follow-up in the elderly LRD group, not reaching statistical difference between the groups (Table 3).

Table 3. Graft function at 1 and 6 months, and 1 and 5 years after kidney transplantation in both groups

	LURD (n^o=15)	LRD>60yr (n^o=18)	
Parameters	**Mean±SD**	**Mean±SD**	**p-value**
sCr 1 month	121,3±33,2	133,8±35,4	ns
sCr 6 months	144,6±46,2	154,9±42,0	ns
sCr 1 year	147,0±53,4	155,6±60,4	ns
sCr 5 years	135,7±48,6	157,9±42,8	ns
cClCr 1 month	67,3±17,7	57,7±13,6	ns
cClCr 6 month	60,7±19,0	58,5±20,1	ns
cClCr 1 year	61,4±22,0	52,5±20,4	ns
cClCr 5 years	55,7±15,6	46,3±16,8	ns

Finally, the graft function 5 years after transplantation did not differ significantly between the groups, although the LURD group maintained slightly higher GFR compared to the elderly LRD group (55,7±15,6 vs. 46,3±16,8 ml/min, p>0,05).

Discussion

Despite the improvement in immunosuppression and better graft and patient survival in cadaver transplantation, the use of living donors for kidney transplantation still results in a slightly superior graft and patient survival, and less morbidity due to fewer rejection episodes, less immunosuppression and better immediate graft function [1,2].
Furthermore, the shortage of cadaveric donor organs and the increasing number of uremic patients on waiting lists prompts transplant centers to examine all possible alternatives in addition to living-related transplantation. Amongst currently avaible options, living donors (related and unrelated) constitute a very useful source of the best quality organs with excellent outcome. Because of the superior outcome of the living compared to the cadaveric donor transplants [3], a greater shift towards living donor transplants is already evident word-wide [12]. Similarly, the same trend has been observed in our unit over the past decades. Furthermore, it has been reported that the majority of living related kidney transplantations are performed from kidneys of siblings and parents, although spousal donation is becoming increasingly more common [13,14].
Tang, *et al.* [13] reported that spousal kidney transplantation shared comparable results with LRD transplantation and should be encouraged in places where cadaveric organs remain scarce. Gjertson and Cecka [15] compared spouse and other genetically unrelated transplants and found no difference in graft survival. In our case study, we could not make such comparison due to the small number of patients in the LURD group.
A number of large single centre studies and registry analyses (United Network of Organ Sharing-UNOS and Australia and New Zeeland Data-ANZDATA) have demonstrated similar graft and patient outcomes between LRD and LURD transplants, even though LURD were more likely to be older donors and often had poorer HLA-matching [12,15,16].
HLA mismatches are known to have an impact on the transplant outcome as shown by the registry data analysis [12,17]. However, many recent single-centre studies have reported similar graft survival rates with LRD and LURD in spite of greater HLA mismatches in LURD transplants [18,19].
On the other hand, Xianming Su, *et al.* (20) examining deceased donor kidney transplants in US, reported that including the provision of safer and more potent immunosuppressive therapy, the significance of HLA matching has diminished, while non-immunological factors continue to impede more marked improvements in long-term graft survival.
In our study, although LURD group had significantly higher HLA mismatches (p<0,01) that might have contributed to the greater number of AR`s observed in this compared to LRD group (p<0,05), they did not have any impact on the graft outcome at 1 and 5 years. However, while HLA mismatches have been reported to have an impact on the long-term graft survival, our study with a mean follow-up of 5 years presents only our short/middle-term results.
Several studies have investigated the prevalence of AR episodes of LURD and LRD recipients. Matas, *et al.* [3] studied ARs occurring after the first 6 months post-transplant and reported rejection rates of 8.6% in LURD an 2,6% in LRD. Fuller, *et al.* [21] reported 1-year AR rates of 30% in LURD an 18,5% in LRD, while in the study of Voiculescu, *et al.* [7] these proportions were found to be even higher-54,2% versus 52,2%, respectively. These finding are in line with the results in our study. Namely, we found significantly higher AR rates of 34,5% in LURD when compared to those of 18,6% in elderly LRD group. Although the AR rates in our study were summarized for the whole follow-up period, AR episodes in both groups occurred predominantly during the first 6 months post-transplant, and only a few of them till the end of the first year post transplantation. In this regard, we could hypo-

thesize that it would be rather strange to have any negative impact on the long-term graft outcome if we had comparable short and mid-term results.

On the other side, it has been well established that the type (live or deceased donor kidneys) and quality (donor age and presence of donor comorbidities) of donor kidneys have a significant impact on renal allograft outcomes. The influence of donor age and recipient age on renal allograft survival has been investigated in numerous studies [16,22,23]. In some of those studies, it has been shown that graft survival of kidneys from old donors (>50-60 years) was significantly reduced as compared to kidneys from younger donors [16,22]. In addition, it has been reported from the same group of authors [16] that the functional graft survival of kidneys from old donors (>60 years) was better in old recipients (>60 years), as compared to all other age groups. Furthermore, in the study of Morales, *et al.* [23] no difference was found in 2-years graft survival between donors more than 5 years younger or older, or in those with age disparity of 10 or 15 years.

In our study, elderly LRD group has been shown to have almost equal graft outcome compared to the LURD group. Hence, although LRD group had lower age matching between the donors and recipients, in contrast and as partial explanation for the similar graft function and outcome between the groups we could consider its higher HLA matching, and lower percentage of AR and UTI.

With regard to the therapy, it has been recently shown that the use of newly proliferation signal inhibitors (PSIs, also known as mTOR inhibitors) which facilitates calcineurin inhibitor (CNI) minimization or withdrawal may be proven as particularly beneficial for "old-for-old" renal transplant recipients [24]. Furthermore, the impact of donor age on development and progression of CAN has been considered as a consequence of several potential risk factors: decreased nephritic mass, increased risk for AR, increased susceptibility for CNI-induced nephrotoxicity and a higher incidence of DGF and hypertension [25-30]. In this regard, the incidence of histological signs of CAN in biopsies performed in the elderly LRD group from our study has been found to be significantly higher when compared to the LURD group.

Fewer studies have analyzed the influence of donor kidney function and subsequent graft function but this influence has been reported as significant [31], modest [32], or even no significant [33]. Lezaic, *et al*. [34] has reported that in recipients without evidence of DGF or AR, the glomerular filtration rate of the donated kidney has no influence on the graft function and survival in LRD recipients. In our study, although the elderly LRD group had a significantly lower estimated GFR of the donated kidney, higher sCr levels and lower cClCr, during the whole period of follow-up, the difference between the groups was not statistically significant. These results might be explained by the fact that while kidney transplantation from unrelated donors was performed with a higher GFR of donated kidney, but in a setting of significantly higher HLA mismatching, the shorter hemodialysis duration and lower incidence of AR and UTI in the group of kidney transplant recipients from older related donors implied almost equal graft outcome and survival. Nevertheless, our outcome and survival rates are valid only in short-term due to the limited period of follow-up, which is the major shortcoming of our study.

Conclusions

The lack of deceased donor organs coupled with the increased utilization of elderly and unrelated live donors have gained a considerable interest in examining the outcome of such grafts. In our study, kidney transplant recipients from LURD have shown comparable 5 years graft survival and outcome to that of LRD older than 60 years. Although these results are obtained in a pilot study, they confirm that in the presence of deceased organ shortage, LURD and older LRD may become a valuable source of potential organ for waitlisted patients for kidney transplantation.

Conflict of interest statement. None declared.

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