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NEPHROLOGY – ORIGINAL PAPER

Effect of donor–recipient age difference on long-term graft survival in living kidney transplantation

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Abstract
Purpose We aimed to examine the influence of donor age on living-donor kidney transplantation (KTx), particularly with regard to long-term graft survival in young recipients with aged kidney grafts.
Methods Between 1988 and 2012, 287 living-donor KTxs were performed in our center. The recipients were divided into 3 groups according to age in years: under 30 (young), 30–49 (middle-aged), and over 50 (old). The data regarding the influence of kidneys from donors aged over 50 years were retrospectively analyzed.
Results Graft survival at 1, 5, 10, and 15 years was 94.7, 94.7, 90.2, and 75.2 %, respectively, in young recipients who received grafts from donors aged under 50 years, and 96.4, 91.9, 65.4, and 41.4 %, respectively, in young recipients who received grafts from donors aged over 50 years ($P = 0.023$). In contrast, there were no significant differences regarding graft survival and donor age in the middle-aged and old recipient groups. Multivariate analysis revealed that young recipient and rejection episode were significant predictors of graft loss in transplantation from older donors. Histological examination revealed significant age-related changes in the grafts before transplant and a significant higher rate of glomerular hypertrophy at the 1-month protocol biopsy in young recipients with aged kidney grafts.
Conclusions Kidney grafts from older living donors affected long-term graft survival in young recipients. In addition to the damage from rejection, aged kidney grafts, which have less nephron mass, may have a limited capacity to appropriately respond to increases in physiological or metabolic demands of young recipients, leading to a greater reduction in renal function.

Keywords Living-donor kidney transplantation · Young recipient · Aged kidney graft · Rejection · Glomerular hypertrophy

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Introduction

In many countries, the lack of donor organs coupled with an increasing number of end-stage renal disease patients has placed greater emphasis on living kidney donation. Along with an improving in long-term graft survival, death with a functioning graft has been increasing, particularly in aged recipients [1–4]. However, patient survival is not the main limitation to long-term graft survival in young recipients, who have a low risk of death after kidney transplantation (KTx).

The adverse impact of increasing donor age on renal allograft survival is well established for deceased donor KTx [4–7]; however, this has not yet been evaluated for long-term graft survival over 10 years in living-donor KTx. Most donors for young recipients are their parents, who belong to the relatively aged donor population.

Thus, the present study aimed to assess graft survival over 20 years in living-donor KTx for young recipients with aged kidney grafts and determine the possible causes for graft loss.

Materials and methods

Patients

A total of 287 living-donor KTxs in Niigata University hospital from 1988 to 2012 were included in this study. The recipients were divided into 3 groups according to their age in years: under 30 (young), 30–49 (middle-aged), and over 50 (old). To investigate the effect of donor age, the donor groups were categorized into 2 groups according to their age in years: younger than 50 years (younger donors) and older than 50 years (older donors). Aged kidney grafts were defined as grafts donated by older donors.

Immunosuppresive therapy

The immunosuppressive therapy commonly used was the triple therapy consisting of a calcineurin inhibitor as the base, a steroid, and an antimetabolite [8]. Mycophenolate mofetil has been used instead of azathioprine and mizoribine since 2001. Basiliximab has been administered since 2002 for induction therapy. In ABO-incompatible KTx, the triple immunosuppresion was given prior to KTx as a desensitization therapy. Rituximab has been used before ABO-incompatible KTx instead of splenectomy since 2004 [8].

Data collection

Recorded baseline data included age, gender, ABO incompatibility, number of human leukocyte antigen (HLA) mismatches, preemptive KTx, biopsy-proven rejection, duration of dialysis, warm and total ischemic times, transplant era, and histological data. The primary clinical outcome of this study was graft survival (death-censored graft survival). Complement-dependent cytotoxicity (CDC) cross-match and flow cytometric cross-match (FCXM) tests were negative before transplantation in all cases of this study. However, panel-reactive antibody (PRA) test was not routinely examined in our hospital. The data were retrospectively analyzed. The present study was approved by the Ethics Committee of Niigata University Faculty of Medicine and conducted in accordance with its ethical principles.

Histological data

Biopsies were performed before transplantation and 1 month after transplantation to evaluate kidney grafts. Mayer's hematoxylin–eosin (HE), alcian blue-periodic acid-Schiff reaction (PAS), and elastic staining were used. In addition to Banff classification, a unique scoring system was used to evaluate kidney grafts in our center. Intimal thickness of the artery and glomerular global sclerosis have been reported to be indicative of age-related changes [9]. To examine the effects of aging in the kidney grafts, the following parameters were analyzed: intimal thickness of interlobular artery (0: no intimal thickness, 1: two layers of internal elastic lamina, 2: three layers, 3: four layers), glomerular global sclerosis (0: 0 %, 1: 0–24 %, 2: 25–49 %, 3: 50–74 %, 4: 75–100 %), and glomerular hypertrophy (0: no glomerular hypertrophy, 1: glomerular hypertrophy). All pathologic specimens were reviewed by one pathologist.

Statistics

Results were expressed as the frequency (percentage) or average (mean) for categorical data. Baseline characteristics between the non-graft loss and graft loss group were compared by Chi-squared analysis or two-sided *t* test. Graft survival estimates were obtained by using Kaplan–Meier methods. To determine the independent predictive variable for graft loss, relevant factors in univariate analysis were fitted into multivariate-adjusted logistic regression analysis. All statistical analyses were performed using SPSS software 15.0 for Windows.

Results

The effect of donor age on long-term death-censored graft survival

The graft survival at 1, 5, 10, 15, and 20 years in the group receiving kidney grafts from young donors aged <50 years

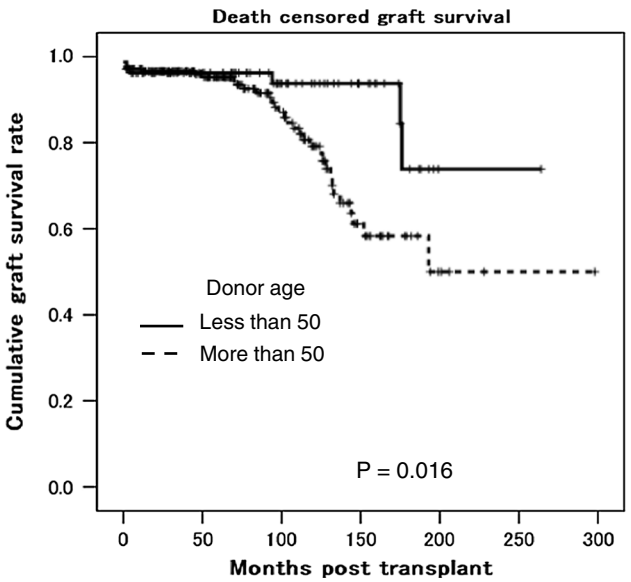

Fig. 1 Kaplan–Meier graft survival by donor age (*black line* donors <50, *dotted lines* donors over 50-year old)

was 96.2, 96.2, 93.8, 73.8, and 73.8 %, respectively (Fig. 1), which was significantly higher than the group receiving grafts from old donors aged over 50 years (97.3, 95.3, 79.1, 58.2, and 49.9 %, respectively; $P = 0.016$). When graft survival was examined for the recipients who received kidney grafts from old donors, no significant differences between the three groups were observed until 8 years after transplantation (84.8 % in young recipients, 91.5 % in middle-aged, and 81.9 % in old). However, the graft survival in young recipients was significantly decreased 9 years after transplantation compared with middle-aged recipients (Fig. 2). Figure 3 shows graft survival for each recipient group. Long-term graft survival with aged grafts was significantly worse only in young recipients ($P = 0.023$).

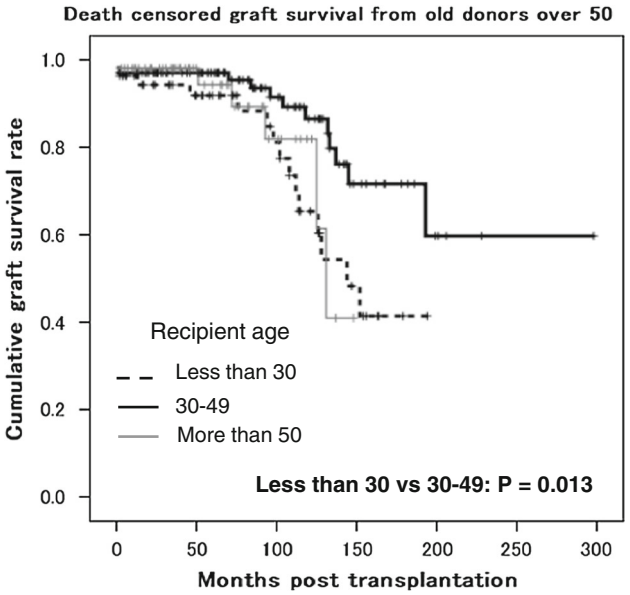

Fig. 2 Kaplan–Meier graft survival in the recipients who received aged kidney grafts over 50 years (*dotted lines* recipient <30, *black line* 30–49, *gray line* over 50-year old)

Risk factors for graft loss in kidney transplant from elderly donors

We first undertook univariate analyses to find out possible risk factors for graft loss in recipients receiving kidney grafts from older donors. Young recipient age, history of rejection, long warm ischemic time, and early transplant era were significantly associated with the higher incidence of graft loss (Table 1). Subsequently, multiple logistic regression analysis was employed to identify independent risk factors for graft loss among these variables. When all the variables were included, just transplant era, which is a persistent factor, was involved in graft loss; without transplant era, young recipient age and history of rejection were risk factors independently associated with graft loss (Table 2).

Age-related changes in kidney grafts

Biopsies before transplantation were performed to evaluate kidney grafts. When we compared the intimal thickness of the interlobular artery and glomerular global sclerosis between the two donor groups, we found histological changes in the aged kidney grafts (over 50 years) before transplantation (Fig. 4a). The average intimal thickness

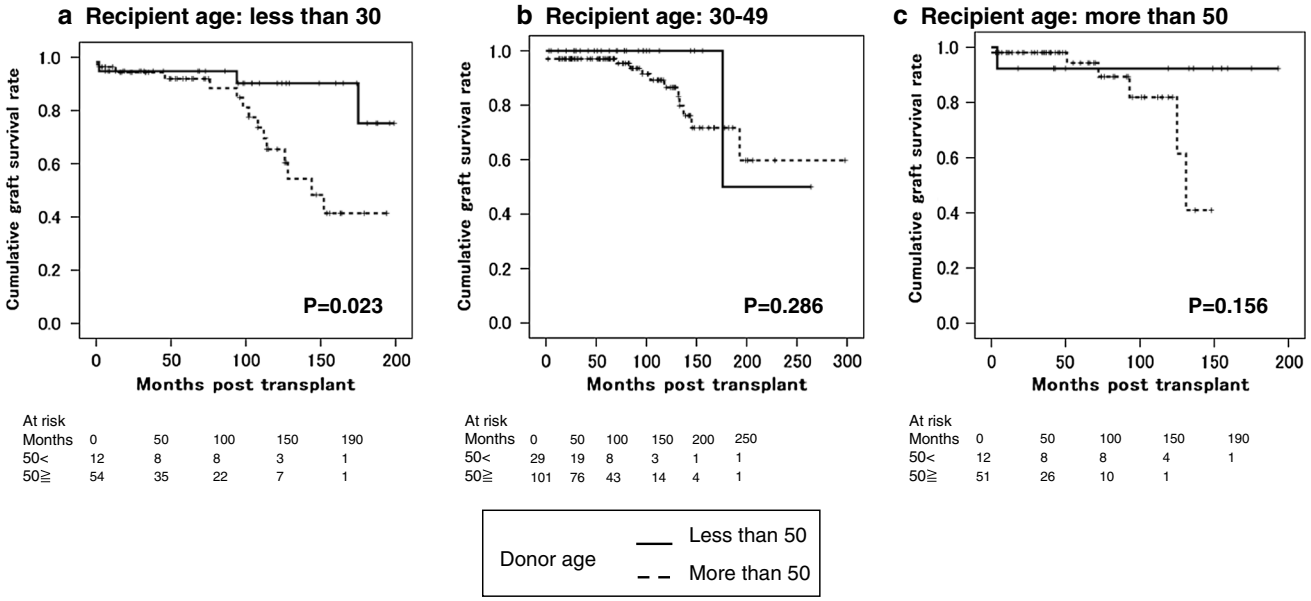

Fig. 3 Kaplan–Meier graft survival in each recipient group. Donor group was divided into two according to their age (*black line* donors <50, *dotted lines* donors over 50-year old)

Table 1 Long-term graft survival predictors in the recipients with aged donors over 50 years by using univariate analysis

Characteristics	Graft loss		*P* value
	−	+	
Recipient age			
<30, *n* (%)	40 (22.9)	15 (44.1)	0.036
30–49, *n* (%)	89 (50.9)	13 (38.2)	
50≥, *n* (%)	46 (26.3)	6 (17.7)	
Male: female, *n*	115:60	23:11	0.828
ABO incompatible, *n* (%)	45 (25.7)	13 (38.2)	0.136
HLA mismatch			
HLA A, mean	0.74	0.59	0.235
HLA B, mean	1.05	0.89	0.158
HLA DR, mean	0.88	0.78	0.382
Preemptive KTx, *n* (%)	35 (20.1)	3 (9.1)	0.134
Rejection episode, *n* (%)	55 (31.6)	23 (71.9)	0.000
Time on dialysis (months)	45.39	44.70	0.956
Total ischemic time (min)	90.85	83.29	0.247
Warm ischemic time (min)	4.89	6.13	0.019
Transplant era			
1988–2000, *n* (%)	31 (17.7)	26 (76.5)	0.000
2001–2012, *n* (%)	144 (82.3)	8 (23.5)	

Table 2 Multivariate logistic regression analysis for graft loss without the factor of transplant era (a) and with all variables (b)

Characteristics	Odds ratio	95 % CI	*P* value
a			
Recipient age <30 years	3.001	1.123–8.016	0.028
Rejection episode	4.401	1.646–11.769	0.003
b			
Recipient age <30 years	2.528	0.934–6.842	0.068
Rejection episode	2.670	0.921–7.737	0.070
Transplant era (before 2001)	2.161	0.038–0.348	0.000

and glomerular global sclerosis score were significantly higher in aged kidney grafts. Thus, significant age-related changes were detectable in kidney grafts before transplantation from old donors. In the 1-month protocol biopsies, glomerular hypertrophy was detected in young recipients who received kidney grafts from older donors (Fig. 4b). In contrast, when the aged kidney grafts were transplanted into old recipients, no increase in glomerular hypertrophy was observed.

Discussion

The effects of donor–recipient age difference and graft survival in living-donor KTx were reported [10, 11]. The results were controversial, and these reports included a range of recipient ages. Our study examined the effects of recipient age coupled with donor age in living-donor KTx and demonstrated that aged kidney grafts affected long-term graft survival in young recipients. Recent reports showed the similar results in living-donor KTx [12, 13]. Living-donor KTx is prevalent in Japan; chances for young recipients to receive kidney grafts from deceased young donors are few. Notably, the reduction in graft survival was particularly apparent after 9 years following transplantation.

When aged kidney grafts were transplanted, young recipient age and rejection episode were significant predictors of graft loss in living-donor KTx. Young recipients had shorter duration of hemodialysis, and they may be immunologically healthier, capable of eliciting a stronger immuno-reaction to donor antigens [14]. Age is inversely correlated with the function of antigen-presenting cells, such as dendritic cells [15]. In addition, aged kidney grafts increased immunogenicity, leading to rejection [16]. In the present study, the donors for 99 % of young recipients with aged kidney grafts were their parents. Parental donors are associated with a higher relative risk of rejection [14]. Although data on the type and severity of the rejection episodes or the treatment and subsequent outcome were not included in the present study, these occurrences resulted in the deterioration of the kidney graft function in young recipients.

In addition to immunological damage to the grafts, non-immunological mechanisms play a role in the pathogenesis of graft loss [17]. The number of nephrons decreases with age [18, 19], and this affects long-term graft survival [20, 21]. Our study showed that significant age-related changes were detected in aged kidney grafts before transplantation. Thus, it is possible that nephron mass reduction and age-related changes in young recipients, who have relatively higher metabolism and muscle, led to glomerular hypertrophy observed at the 1-month protocol biopsies in our study. Unfortunately, biopsies could not be performed in all recipients because of complications and/or bleeding tendencies. Therefore, histological data could not be analyzed with graft survival. However, this is the first report to investigate the relationship between the age-related changes of the grafts and graft survival in young recipients.

Considering the recent advances in immunosuppressive therapy, early transplant era is the strongest factor associated with poorer functional outcomes also in the present study; still, young recipient age and rejection episode were of borderline significance. Further studies will be necessary to verify the effect of donor age on outcomes of young recipients with the recent immunosuppressive therapy.

In conclusion, aged kidney grafts affected long-term graft survival in young recipients. With the current lack of

a Intimal thickness of interlobular artery

Score	Donor<50 y.o	Donor≧50 y.o
0	45	85
1	8	19
2	0	7
3	0	3

Glomerular global sclerosis

Score	Donor<50 y.o	Donor≧50 y.o
0	32	46
1	26	68
2	0	10
3	0	2
4	0	0

b

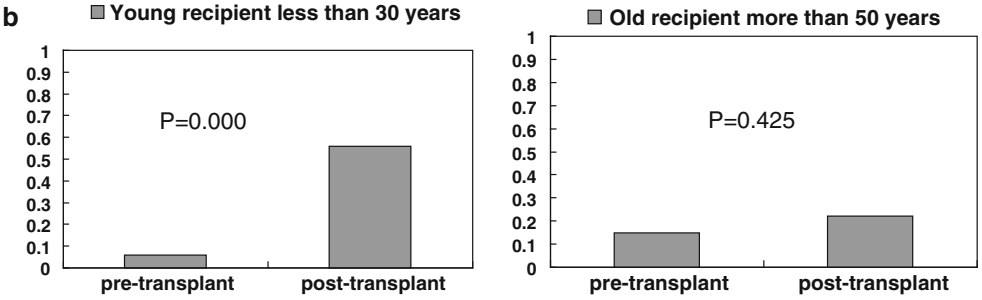

Fig. 4 **a** Age-related changes in kidney grafts pre-transplant. **b** Glomerular hypertrophy at the 1 month post-transplantation

organs, we should not limit the opportunities of KTx for young recipients from older donors. However, we may need to improve the long-term graft survival with the usage of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors to reduce glomerular hypertrophy. Powerful immunosuppresive therapy may also help to reduce the rejection rate in young recipients with aged kidney grafts. Furthermore, drug monitoring is essential for young recipients who have a relatively high risk of drug non-adherence.

Conflict of interest None.

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