# Kidney Transplantation from Living Donors: Comparison of Results between Related and Unrelated Donor Transplants under New Immunosuppressive Protocols

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**Key words:** kidney transplantation, donor, graft, survival

## Abstract

**Background:** Recent advances in immunosuppressive therapy have led to a substantial improvement in the outcome of kidney transplantation. Living unrelated donors may become a source of additional organs for patients on the kidney waiting list.

**Objectives:** To study the impact of the combination of calcineurin inhibitors and mycophenolate-mofetile, together with steroids, on outcomes of living related and unrelated transplants.

**Methods:** Between September 1997 and January 2000, 129 patients underwent living related (n = 80) or unrelated (n = 49) kidney transplant. The mean follow-up was 28.2 months. Immunosuppressive protocols consisted of MMF with cyclosporine (41%) or tacrolimus (59%), plus steroids. Patient and graft survival data, rejection rate, and graft functional parameters were compared between the groups.

**Results:** LUD recipients were older (47.8 vs. 33.6 years) with a higher number of re-transplants (24.5% vs. 11.2% in LRD recipients, $P < 0.05$). Human leukocyte antigen matching was higher in LRD recipients ($P < 0.001$). Acute rejection developed in 28.6% of LUD and 27.5% of LRD transplants ($P$ = NS). Creatinine levels at 1, 2 and 3 years post-transplant were 1.6, 1.7 and 1.7 mg/dl for LRD patients and 1.5, 1.5 and 1.3 mg/dl for LUD recipients ($P$ = NS). There was no difference in patient survival rates between the groups. One, 2 and 3 year graft survival rates were similar in LRD (91.3%, 90% and 87.5%) and LUD (89.8%, 87.8% and 87.8%) recipients.

**Conclusions:** Despite HLA disparity, rejection and survival rates of living unrelated transplants under current immunosuppressive protocols are comparable to those of living related transplants.

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Advances in immunosuppressive therapy during the last two decades have led to substantial improvements in the outcome of kidney transplantation. Unfortunately, with the growing number of transplant candidates and an unchanged supply of cadaver kidneys, there is a severe organ shortage and an extended waiting time for transplant [1]. In Israel, the number of cadaver transplants performed (approximately 100/year) are far below the number of patients on the waiting list (594 patients) [2]. Furthermore, it has been estimated that even under the most efficient system of organ retrieval, the pool of cadaver donors may never be sufficient to satisfy the growing demand [3]. Several solutions to this problem have been suggested, including expansion of the organ pool by use of kidneys from "marginal" donors, transplantation of kidneys donated by living unrelated donors, and use of kidneys from non-heart-beating donors [4,5]. Although all of these approaches have been applied, none has yet successfully narrowed the gap between supply and demand of kidneys for transplant.

Living unrelated transplantation was pursued in several centers worldwide with excellent long-term results, equaling those of one-haplotype-matched living related transplantation and superior to the results of cadaver transplantation [6–14]. Although these studies analyzed long-term graft and patient survivals, only a few addressed other transplant-associated parameters like immediate graft function, frequency and severity of acute rejections, etc. We report here on our 3 year, single-center experience with 129 living kidney transplants. Early postoperative functional parameters, frequency and severity of acute rejections, and graft and patient survival data were analyzed with an emphasis on the comparison of living related and unrelated kidney transplantation

## Patients and Methods

Between September 1997 and January 2000, 129 living kidney transplants were performed at the transplant department of Rabin Medical Center. Of these, 80 recipients (62%) were transplants using grafts from living related donors and 49 (38%) from a genetically unrelated donor. The LRDs were parents (55%), siblings (36%), offspring (6%), and distant relatives (3%). The majority of unrelated donors were spouses (51%) or friends (37%); crossover transplants were done between the spouses of two couples, and another two were altruistic donations. Altogether, 108 recipients (84%) received a first kidney graft and 21 (16.3%) underwent re-transplant of a second graft, 18 (14%) a third, 2 (1.5%) a fourth, and 1 (0.8%) a fifth graft.

Living unrelated donation was considered if a suitable genetically related donor was not available. According to the regulations of the Israel Transplant Organization, potential living

MMF = mycophenolate-mofetile
LUD = living unrelated donor
LRD = living related donor
HLA = human leukocyte antigen

donations were approved by the hospital ethics committee as well as by the national transplant organization. In unrelated transplants, in addition to the regular procedure, a Ministry of Health ethics committee approved donation after verifying that the donation act was voluntary and uncompensated.

All transplants were ABO-compatible with a negative cross-match. Donor-specific blood transfusions were never used prior to transplantation. Standard triple immunosuppressive protocols with cyclosporine-neoral or tacrolimus, mycophenolate mofetil and prednisone were employed. Immunosuppressive doses were adjusted to achieve CyA trough whole blood levels of 200–300 ng/ml (Abbott TDx assay) and tacrolimus trough levels of 10–15 pg/ml (Abbott Tacrolimus, MEIA assay). Overall, 41% of recipients received a CyA-based immunosuppressive regimen and 59% were on a tacrolimus-based protocol. The proportion of patients on each regimen was similar between the living related and unrelated groups [Table 1].

Acute rejection was diagnosed clinically and was confirmed by a fine needle aspiration and/or a core biopsy scored according to the Banff criteria [15]. Rejection episodes were treated with a bolus of 500 mg methylprednisolone per day for 3 days. Patients with steroid-resistant rejections were given polyclonal antibodies (ATG) or monoclonal anti-T cell antibodies ($OKT_3$) if they did not respond to the first few doses of ATG. Clinical severity of rejection was classified as mild (requiring only steroid bolus), moderate (requiring ATG), or severe (requiring $OKT_3$). Patients were followed for a mean of 28.2 months (range 12–51). The following parameters were compared between the two groups: rejection rate and severity, rate of post-transplant acute tubular necrosis, serum creatinine levels at different post-transplant intervals (7 and 30 postoperative days and 6, 12, 24 and 36 months) and graft and patient survivals.

CyA = cyclosporine-neoral

**Table 1.** Demographic and clinical data of patients from living-related and living-unrelated donors

| | Living related donor (%) | Living unrelated donor (%) |
|---|---|---|
| Patients (n) | 80 (62) | 49 (38) |
| Recipient gender | | |
| Male | 57 (71.2) | 37 (75.5) |
| Female | 23 (28.8) | 12 (24.5) |
| Mean age (±SD) | | |
| Donor | 47.612 | 44.3±11.3 |
| Recipient | 33.6±15* | 47.8±12 |
| Diabetes mellitus | 4 (5) | 7 (14.2) |
| Pre-transplant dialysis | 73 (91) | 47 (96) |
| Transplantation | | |
| Primary | 71 (88.8) | 37 (75) |
| Re-transplant | 9 (11.2)** | 12 (24.5) |
| Mean no. of mismatches | 2.39±1.4* | 4.12±1.3 |
| Immunosuppression | | |
| CyA-MMF-steroids | 32 (40) | 21 (42) |
| Tacrolimus-MMF-steroids | 48 (60) | 28 (57.5) |
| No of acute rejections | | |
| 0 | 58 (72.5) | 35 (71.4) |
| 1 | 18 (22.5) | 12 (24.5) |
| 2 | 4 (5) | 2 (4.1) |
| Rejection severity | | |
| Mild | 12 (54.5) | 4 (28.6) |
| Moderate | 6 (27.3) | 7 (50) |
| Severe | 4 (18.2) | 3 (21.4) |

* $P < 0.001$.
** $P < 0.05$.

## Statistical analysis

Continuous variables were compared using Student's *t*-test. Parametric variables were analyzed by chi-square or Fisher's exact tests. The Cox proportional hazards model was used for the whole patient cohort to define the risk factors for patient death and graft loss (including by death). Patient and graft survivals were calculated using the Kaplan-Mayer method. Survival was compared between groups using the log-rank test. Statistical analysis was performed with the SAS software for Windows, version 6.12 (Cary, NC, USA).

## Results

Donor and recipient characteristics for the two groups are presented in Table 1. The mean donor ages were 47.6 ± 12 and 44.3 ± 11.3 years in the LRD and LUD groups, respectively (not significant). The mean recipient age in the LUD group (47.8 ± 12 years) was significantly higher than in the LRD group (33.6 ± 15 years, $P < 0.001$). More patients in the LUD group were diabetic (14.2% vs. 5%, $P$ = NS) and recipients of a re-transplant (25% vs. 11.2%, $P < 0.05$). Similar proportions of patients in both groups were on dialysis at the time of transplant. Living related and unrelated groups differed significantly in the number of HLA mismatches (2.4 vs. 4.1 respectively, $P < 0.001$).

Post-transplant, the incidence of delayed graft function was not different between the groups. The incidence of biopsy-proven acute rejection was 27.5% in the LRD group and 28.6% in the LUD group ($P$ = NS). Of these, 12.5% and 20.4% were steroid-resistant rejections in the LRD and LUD groups, respectively ($P$ = NS). Patients in the LUD group tended to require more aggressive treatment for steroid-resistant rejection, although there was no statistical difference in severity of rejection between the groups. Four patients (18.3%) in the LRD and three (21.4%) in the LUD groups required $OKT_3$ treatment for severe rejection. The mean serum creatinine levels at various intervals post-transplant were not different between the groups [Figure 1]. Creatinine levels at 1, 2 and 3 years post-transplant were 1.63 ± 0.4, 1.73 ± 0.7 and 1.7 ± 0.3 mg/dl for LRD, and 1.48 ± 0 .3, 1.48 ± 0.4 and 1.32 ± 0.5 mg/dl for LUD recipients, respectively ($P$ = NS).

Nine patients died: 5 (6.3%) from the LRD group and 4 (8.2%) from the LUD group ($P$ = NS). Causes of death were myocardial infarction in three recipients and sepsis in six. The patients died on the fourth and fifth POD, 7.5, 9 months; and 0.5, 8, 9, 24 and 39 months post-transplant in the LUD and LRD groups, respectively. Overall 1, 2 and 3 year patient survival was 94.6%, 93.8% and 93%, respectively. There was no difference in patient survival rates between the LRD (96.3%, 95% and 93.8%) and LUD (91.8%, 91.8%

POD = postoperative day

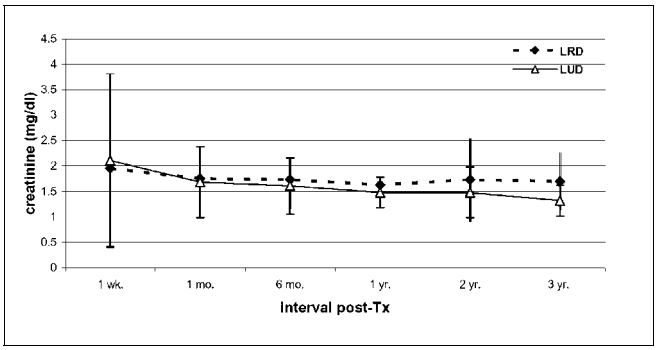


**Figure 1.** Mean serum creatinine levels after kidney transplantation.

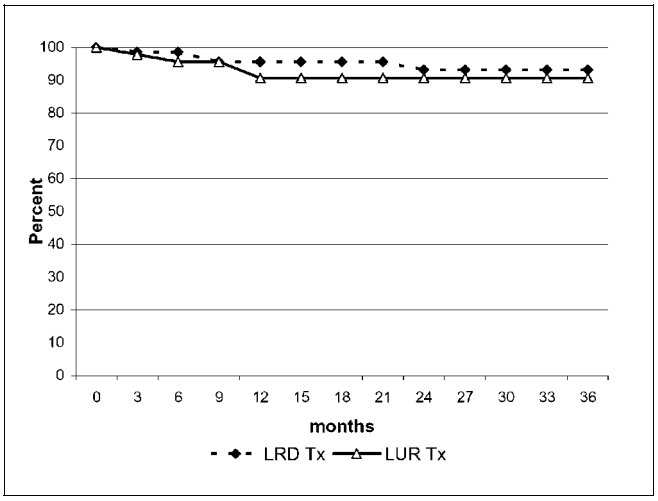


**Figure 2.** Kaplan-Meier curves for patient survival.

and 91.8%) recipients [Figure 2]. Seven patients lost their grafts and returned to dialysis: 5 (6.3%) in the LRD and 2 (4.1%) in the LUD groups. The reasons for graft loss were: vascular thrombosis on the first POD and chronic rejection in the 19th post-transplant month in the LUD group; vascular thrombosis (n=3, on 1–2 PODs), acute rejection (8th POD), and chronic rejection (32th month post-transplant) in the LRD group. The overall 1, 2 and 3 year graft survivals were 90.7%, 89.1% and 87.6%, respectively. The graft survival rates did not differ in the LRD (91.3%, 90% and 87.5%) and LUD (89.8%, 87.8% and 87.8%) recipients [Figure 3].

In the Cox-hazard regression model including all patients, the factors associated with patient death were: increasing age of the recipient (odds ratio 1.1, $P = 0.0012$) and re-transplantation (OR 9.7, $P = 0.0073$). Similarly, graft survival was negatively affected by recipient age (OR 1.1, $P = 0.042$) and re-transplantation (OR 9.6, $P = 0.0035$).

## Discussion

Unrelated kidney transplantation was first undertaken in the early 1960s when dialysis therapy was not routinely available [16]. The donors, spouses or in-laws were emotionally related to the recipients. In that era, although survival rates after living unrelated

OR = odds ratio

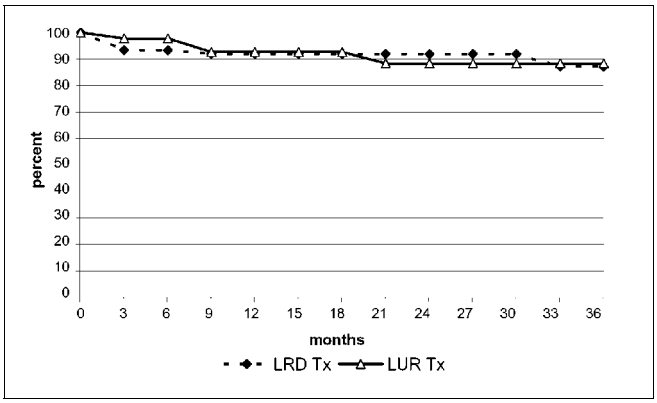


**Figure 3.** Kaplan-Meier curves for graft survival.

and cadaver kidney transplants were similar, they were still far below survival rates following living related transplantation [17]. During the subsequent 20 years, most transplant centers abandoned living unrelated transplantation due to ethical issues of unrelated donation and the increasing availability of dialysis therapy. Theoretically, because of the stable health of the donor and the short ischemic time, living unrelated transplant should be advantageous over the cadaver transplant. It is possible that the inefficient immunosuppression was probably the main explanation for the poor results in the initial experience with living unrelated transplantation and, indeed, in more recent reports the results are not different from those of living related transplantation [18–20]. In 1996, the United Network for Organ Sharing Scientific Renal Transplant Registry reported that 1 year survival rates of grafts from 1-haplotype-matched siblings and unrelated donors were identical (92%), and better than those of cadaver kidney transplants (84%). Similarly, at 3 years, graft survival rates of spousal (85%) and other unrelated (81%) transplants were in the range of 1-haplotype-matched living donor transplants (82%) and significantly higher than the results of cadaver transplants (70%) [7].

The advantage of living unrelated over cadaver kidney transplantation is maintained over the long term. In a series from the Washington University School of Medicine, the 5 year graft survival rate of living unrelated transplants was 85.9% compared to 70.7% in the cadaver donor group [8]. In a report from the University of Wisconsin, there was no difference in 10 year graft survival between haploidentical related (59%) and unrelated (56%) living transplants [9]. Similarly, a recent study from the University of California shows that long-term survival and graft half-lives of living unrelated transplants are comparable to those of parent donor grafts and significantly better than the cadaver grafts [12].

In our series we also noted similar graft and patient survivals after living related and unrelated transplantation in the short and mid-term. But, as important, we showed also that despite a higher immunologic risk, as evident by significant HLA-mismatching and higher proportion of patients undergoing retransplantation in the living unrelated group, the incidence and severity of acute rejections were similar in both groups. We also noted similar immediate and late graft function in recipients of the two groups, a finding that might predict similar long-term outcome. Our results, along with recent reports from other centers may suggest that in the

present era, unlike in the cadaver transplant setting, genetic disparity may not play such an important role impacting outcome in living donor transplantation. The short cold-ischemia in the living donor transplant setting along with potent immunosuppressive regimens may mask the disadvantage of HLA-mismatching, although studies with a longer follow-up and a larger patient cohort are needed to confirm this statement.

An important barrier to widespread implementation of living unrelated transplantation is the ethical issue [21]. In a survey of professionals from different U.S. transplant centers, 90% theoretically supported the use of spouses and 60% the use of friends as donors [22]. In Israel, living unrelated transplantation was legally approved in 1996 and any transplant has to be authorized by a Ministry of Health ethics committee following a psychosocial evaluation performed by professionals outside the hospital. Nevertheless, even under the strictest law, it is hard to guarantee that all unrelated donations are truly altruistic acts. On the other hand, because of the limited organ supply there is a worldwide growth in the number of commercial transplants and a shift in society towards accepting organs as a commodity that can be paid for [23]. Based on medical suitability of unrelated donation and in order to avoid further commercialization of kidney transplantation, it is suggested that lawyers, medical professionals and ethicists act soon to regulate unrelated compensated transplantation [24].

In conclusion, our study has shown that under current immunosuppressive protocols, kidney transplantation from living unrelated donors can achieve results as good as those of living related transplantation. In light of the increasing organ shortage, this donor pool should be more widely used under careful and strict guidelines, while at the same time preventing the growth of illegal organ trade.

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## References

1. Ratner LE. Report card on living kidney donation. *Am J Transplant* 2003;3:771–3.
2. Data from Israel Transplant Center report, Ministry of Health, 2003.
3. Evans R. Need, demand and supply in kidney transplantation: a review of the data, an examination of the issues and projections through and the year 2000. *Semin Nephrol* 1992;12:234–55.
4. Youngner SJ, Arnold RM. Ethical, psychosocial and public policy implications of procuring organs from non-heart-beating cadaver donors. *JAMA* 1993;269:2769–74.
5. Spital A. Unconventional living kidney donors – attitudes and use among transplant centers. *Transplantation* 1989;48:243–8.
6. Terasaki PI, Cecka MJ, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med* 1995;333:333–6.
7. Cecka JM. The UNOS Scientific Renal Transplant Registry. *Clin Transplant* 1996;1–14.
8. Lowell JA, Brennan DC, Shenoy S, et al. Living-unrelated renal transplant provides comparable results to living related renal transplant: a 12-year single-center experience. *Surgery* 1996;119:538–43.
9. D'Alessandro AM, Pirsch JD, Knechtle SJ, et al. Living unrelated renal donation: the University of Wisconsin experience. *Surgery* 1998;124:604–11.
10. Humar A, Durand B, Gillingham K, Payne WD, Sutherland DE, Matas AJ. Living unrelated donors in kidney transplants: better long-term results than with non-HLA-identical living related donors? *Transplantation* 2000;69:1942–5.
11. Ishikawa N, Tanabe K, Tokumoto T, et al. Long-term results of living unrelated renal transplantation. *Transplant Proc* 1999;31:2856–7.
12. Cecka JM. Kidney transplantation from living unrelated donors. *Annu Rev Med* 2000;51:393–406.
13. Gjertson DW, Cecka JM. Living unrelated kidney transplantation. *Kidney Int* 2000;58:491–9.
14. Samhan M, Al-Mousawi M, Al-Sweih N, Reshaid W, AbdulHalim M, Johny KV. Renal transplantation from living unrelated donors. *Transplant Proc* 2001;33:2642–3.
15. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 classification of renal allograft pathology. *Kidney Int* 1999;55:713–23.
16. Kuss R. Human renal transplant memories, 1951 to 1981. In: Terasaki PI, ed. History of Transplantation: 35 Years Recollection. Los Angeles: UCLA Tissue Typing Laboratory, 1991:39.
17. Starzl T, Porter K, Andres G, et al. Long-term survival after renal transplantation in humans (with special reference to histocompatibility matching, thymectomy, homograft glomerulonephritis, heterologous ALG, and recipient malignancy). *Ann Surg* 1970;172:437–72.
18. Wyner L, Novick A, Streem S, Hodge EE. Improved success of living unrelated renal transplantation with cyclosporine immunosuppression. *J Urol* 1993;149:706–8.
19. Ossareh S, Ghods AJ. Spousal renal transplantation – single-center experience. *Transplant Proc* 1999;31:3121.
20. Binet I, Bock AH, Vogelbach P, et al. Outcome in emotionally related living kidney donor transplantation. *Nephrol Dial Transplant* 1997;12:1940–8.
21. Fellner SK, Thistlethwaite JR, Stuart FP. Kidney transplantation from unrelated living donors [Letter]. *N Engl J Med* 1986;315:713.
22. Spital A. Do U.S. transplant centers encourage emotionally related kidney donation? *Transplantation* 1996;61:374–7.
23. Phadke KD, Anandh U. Ethics of paid organ donation. *Pediatr Nephrol* 2002;17:309–11.
24. Friedlander MM. The right to sell or buy a kidney: are we failing our patients? *Lancet* 2002;359:971–3.

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