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HIGH SURVIVAL RATES OF KIDNEY TRANSPLANTS FROM SPOUSAL AND LIVING UNRELATED DONORS

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Abstract *Background.* In the United States, increasing numbers of persons are donating kidneys to their spouses. Despite greater histoincompatibility, the survival rates of these kidneys are higher than those of cadaveric kidneys. We examined the factors influencing the high survival rates of spousal-donor kidneys.

Methods. Kidney-transplant data from the United Network for Organ Sharing Renal Transplant Registry were used to calculate graft-survival rates with Kaplan–Meier analysis.

Results. The three-year survival rates were 85 percent for kidneys from 368 spouses, 81 percent for kidneys from 129 living unrelated donors who were not married to the recipients, 82 percent for kidneys from 3368 parents, and 70 percent for 43,341 cadaveric kidneys. The three-year survival rate for wife-to-husband grafts was 87 percent, which was the same as for husband-to-wife grafts if the wife had never been pregnant.

If the wife had previously been pregnant, the three-year graft-survival rate was 76 percent ($P=0.40$). The three-year graft-survival rate among recipients of spousal grafts who did not receive transfusions preoperatively was 81 percent, as compared with 90 percent for recipients who received 1 to 10 transfusions preoperatively ($P=0.008$). The superior survival rate of grafts from unrelated donors could not be attributed to better HLA matching, white race, younger donor age, or shorter cold-ischemia times, but might be explained by damage due to shock before removal in 10 percent of the cadaveric kidneys.

Conclusions. Spouses are an important source of living-donor kidney grafts because, despite poor HLA matching, the graft-survival rate is similar to that of parental-donor kidneys. This high rate of survival is attributed to the fact that the kidneys were uniformly healthy. (*N Engl J Med* 1995;333:333-6.)

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.¹⁻⁹ Although most transplants from living unrelated donors are mismatched for HLA antigens, the survival rates of these grafts are higher than those of similarly mismatched cadaveric grafts.¹⁰ As a result, increasing numbers of transplantations involving grafts from living unrelated donors have been performed recently in the United States. In this report, we analyze the factors that contribute to the high success rate of grafts from unrelated donors.

METHODS

Kaplan–Meier curves and log-rank tests were used to describe and compare the survival rates of grafts from 368 spouses, 129 living unrelated donors, 3368 parents, 1984 HLA-identical siblings, 1411 offspring, and 43,341 cadavers from the United Network for Organ

Sharing (UNOS) Renal Transplant Registry and to evaluate the effect of donor-kidney characteristics on survival. The status of the 129 living unrelated donors was reconfirmed from a separate questionnaire, because the data-collection forms did not clearly exclude distant relatives from being living unrelated donors. Transplants from spouses were analyzed separately from transplants from unrelated donors who were not married to the recipients. There were no exclusions, and deaths of recipients were counted as graft losses. All *P* values were two-sided.

There were differences between spousal and cadaveric grafts with respect to covariates known to influence graft survival. For example, only 7 percent of the spousal transplants did not function immediately, as compared with 26 percent of the cadaveric transplants, as measured by the lack of urine output within 24 hours or the need for dialysis within one week after transplantation. Other covariates of interest included the recipient's race, the donor's age, and the degree of HLA mismatching. To illustrate, recipients of spousal grafts, as compared with recipients of cadaveric grafts, were less often black (6 percent vs. 22 percent), had a higher average number of HLA mismatches (4.2 vs. 3.6 antigens mismatched), and were younger (31 vs. 42 years of age).

To account for these differences, two logistic-regression models were used to assess the joint effects of donor type (spousal vs. cadaveric), early functional status, recipient's race, donor's age, and numbers of HLA mismatches on the probability of graft failure one and three years after transplantation. The analysis was performed with the Stata statistical computer program¹¹ as described previously.¹² To gauge differences among transplantations whose success was not compromised by other factors, one- and three-year rates of survival for spousal and cadaveric transplants were adjusted to values representative of the optimal outcome level of the remaining covariates.

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The results indicated that a non-black recipient of a kidney with good early functioning and 0 HLA mismatches from his or her 31-year-old spouse could expect graft-survival rates of 95 percent at one year and 93 percent at three years. Similar recipients of cadaveric transplants could expect graft-survival rates of 91 percent at one year and 86 percent at three years. These differences in adjusted survival rates between spousal and cadaveric grafts at one and three years were very similar to the corresponding differences in the unadjusted rates between spousal grafts and cadaveric transplants with good early functioning, as shown in Figure 1. As a result of this close agreement, appropriately stratified univariate methods were deemed statistically sufficient, and further discussion regarding the multifactor analysis is omitted.

RESULTS

The grafts from HLA-identical siblings had the highest survival rates (Fig. 1). The survival rate of parental-donor grafts with one HLA-haplotype mismatch at three years was 9 percentage points lower than that of grafts from HLA-identical siblings. The survival rates of both spousal grafts and grafts from other living unrelated donors with two HLA-haplotype mismatches were similar to that for parental-donor grafts with one HLA-haplotype mismatch rather than that for cadaveric grafts with two HLA-haplotype mismatches. Despite the fact that the HLA matching was better for the cadaveric grafts (average number of HLA-A, B, and DR mismatches, 3.6) than for spousal grafts and grafts from other living unrelated donors (average number of HLA-A, B, and DR mismatches, 4.1), the survival of the cadaveric grafts was poorer.

The number of HLA mismatches expected on a random basis was computed to be 4.5 on the basis of random pairings of donors and recipients. Thus, there was some small degree of selection against poorly mismatched pairs in the spousal and nonspousal unrelated transplant groups. The level of HLA matching for the cadaveric grafts was higher, as a result of kidney allocation under the UNOS point system, which encourag-

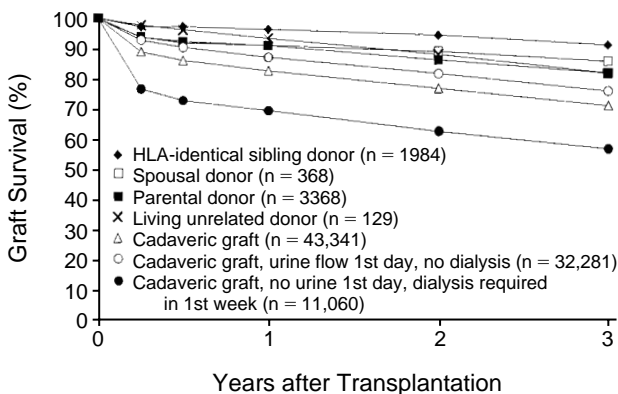


Figure 1. Survival of First Kidney Grafts.

The HLA-identical siblings were matched to the patients for all six of the HLA-A, B, and DR loci. The cadaveric grafts were further grouped according to whether recipients had diuresis on the first day after transplantation and did not require dialysis or had no first-day urine flow and required dialysis within the first week. The living unrelated donors did not include spouses and were confirmed to be unrelated to the recipients on the basis of a questionnaire.

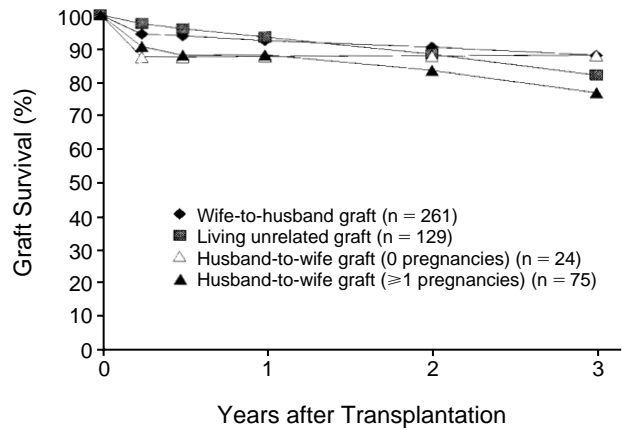


Figure 2. Graft Survival among Recipients of Kidneys from Spousal Donors.

Husband-to-wife grafts were subgrouped according to whether the wife had previously been pregnant. For eight of the wives, the number of pregnancies was not known.

es better-matched transplants. Thus, the higher rate of survival of spousal grafts and grafts from other living unrelated donors as compared with cadaveric grafts cannot be attributed to superior matching.

The survival of grafts from unrelated donors was comparable to that of parental-donor grafts despite the average of 4.1 HLA mismatches in the former group, as compared with 2.3 HLA mismatches in the latter group. Therefore, the high rate of survival of the unrelated-donor grafts was not due to HLA matching that was similar to that of the parental-donor grafts. Nevertheless, there was an effect of HLA matching on the survival of spousal grafts; no rejections occurred before hospital discharge in 93 percent of the recipients of spousal grafts with no HLA-DR mismatches, in 77 percent of the recipients of grafts with one HLA-DR mismatch, and in 70 percent of the recipients of grafts with two HLA-DR mismatches.

The survival rates of cadaveric grafts that functioned from the first day, so that the recipient did not require dialysis, approached those of grafts from living unrelated donors (Fig. 1). Cadaveric grafts that failed to function immediately or in which function was delayed, so that the recipient required dialysis in the first week, had a lower survival rate. These results indicate that some of the cadaveric grafts were damaged. When they were removed from the analysis, the survival rate approached that of grafts from living unrelated donors.

The three-year survival rate of spousal grafts was 85 percent. Among the spousal donors, 2.6 times as many wives as husbands were donors (Fig. 2). The survival rates of wife-to-husband grafts were the same (87 percent) as those of husband-to-wife grafts if the wife had not been pregnant. However, if the wife had been pregnant, graft survival was worse but not significantly so (76 percent, P=0.40). Among the wives, 21 percent were immunized, as indicated by serum reactivity to lymphocytes of more than 10 percent of randomly chosen persons. This rate of reactivity may be low because

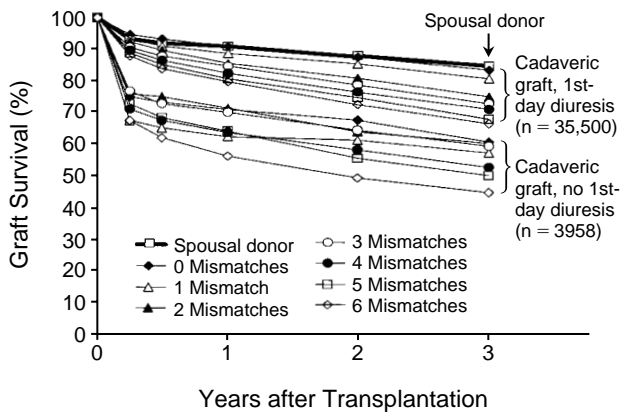


Figure 3. Survival of First Cadaveric Grafts According to Urine Flow on the First Day.

The grafts were further grouped on the basis of the number of HLA-A, B, and DR mismatches. The spousal-donor group is included for comparison.

wives with reactivity to their husbands' lymphocytes may have been excluded from consideration for transplantation. Reactivity status notwithstanding, the graft outcome was not different between wives who were sensitized and those who were not ($P=0.65$).

A comparison of the survival of grafts from unrelated donors with the survival of grafts from recipients' children revealed that the three-year survival of 696 offspring-to-mother grafts was 80 percent, as compared with 82 percent for 99 husband-to-wife transplants. In addition, for 715 offspring-to-father grafts, the three-year graft survival was 84 percent, as compared with 87 percent for 261 wife-to-husband grafts. Thus, the survival rates of spousal grafts from biologically unrelated persons were similar or even slightly higher than those of the offspring-to-parent grafts with one HLA-haplotype mismatch. Among the spousal grafts, the three-year survival rates were 86 percent in the 290 white recipients and 82 percent in the 78 black recipients.

The effect of HLA matching on cadaveric grafts grouped according to whether diuresis occurred on the first day after transplantation is shown in Figure 3. Only among the uncompromised cadaveric grafts with 0 HLA-A, B, and DR mismatches were the survival rates similar to those of the spousal grafts. Regardless of the degree of matching, the survival rates of grafts that functioned on the first day were higher than the rates of those that did not. The survival rate of grafts mismatched for all six antigens that functioned on the first day was higher than that of a perfectly matched graft that did not function immediately. Thus, the survival rate of compromised grafts, despite their

being HLA-matched, was lower than that of a poorly matched graft that functioned immediately. Nevertheless, there was a stepwise gradation in graft survival according to the degree of mismatching for cadaveric grafts regardless of functional status on the first day, indicating that HLA matching was still valuable for all categories of cadaveric transplants.

Preoperative transfusions increased the three-year rate of survival of spousal grafts: the rate was 81 percent for the 188 recipients who did not undergo transfusion and 90 percent for the 167 who received 1 to 10 transfusions ($P=0.008$). In this analysis, 13 recipients who received more than 10 transfusions were excluded since their high transfusion requirement may have reflected the presence of other medical complications.

Since the living unrelated donors were younger than the typical cadaveric donors, we compared the rate of graft survival according to donor's age (Fig. 4). The survival rates of grafts from living donors were higher than those of cadaveric grafts within each age category.

Short periods of cold ischemia of three to six hours among 1394 cadaveric grafts led to a one-year graft-survival rate of 80 percent, as compared with 91 percent among spousal grafts. Among 5308 cadaveric grafts subjected to 6 to 12 hours of cold ischemia, the one-year graft-survival rate was 84 percent; among 18,383 grafts subjected to 12 to 24 hours of cold ischemia, the rate was 83 percent. Thus, graft survival was not influenced markedly by cold-ischemia times of less than 24 hours.

DISCUSSION

Our results demonstrate that kidney grafts from living unrelated donors have high survival rates, despite a higher degree of HLA mismatching than is found in cadaveric grafts. The length of cold ischemia was not an

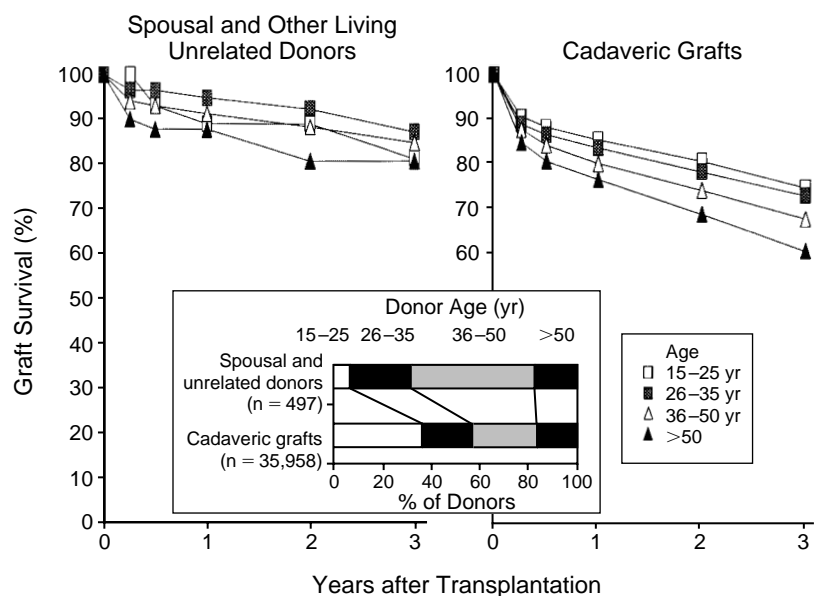


Figure 4. Survival of Kidney Grafts According to Donor Age. The age distribution of the donors is shown in the inset.

important factor. The receipt of preoperative transfusions was associated with higher rates of graft survival, but survival rates among recipients of spousal grafts who had not received transfusions were higher than those among recipients of cadaveric grafts. A center effect was unlikely to be the source of the difference, because the transplantations were performed at 97 transplantation centers in the United States. Compliance with respect to taking immunosuppressant drugs may be higher among recipients of spousal grafts because the recipient lives with the donor. This probably is not the only explanation, because the survival rates of grafts from other living unrelated donors were similarly high.

We think that the crucial difference in survival between living unrelated grafts and cadaveric grafts is that about 10 percent of the cadaveric grafts are damaged before removal, as indicated by the 10 percent difference in graft-survival rates. Once the total nephron mass is compromised, hyperfiltration of the remaining nephrons ultimately leads to graft failure,^{10,13} but this important cause of failure is usually not recognized, and the failure instead is often attributed to chronic rejection.¹⁰ Evidence that chronic kidney rejection is dependent on renal mass was demonstrated in rats, which had a lower rate of chronic rejection when an additional allografted kidney was implanted and a higher rate when kidneys that were reduced in size were implanted.¹³

Spouses represent an important potential new source of kidney grafts. Among the 25,000 patients waiting for a kidney transplant, approximately 95 percent are over the age of 20 years. If 50 percent of the 23,500 adults are married, as many as 11,750 could have a potential spousal donor. The number of potential spousal donors who may become actual donors can be estimated from a previous study of potential living related donors, in which 57 percent became actual donors.¹⁴ If the same proportion of 11,750 potential spousal donors become actual donors, then 6697 donors would be available.

It appears now that ABO incompatibility can be overcome with the use of immunoadsorption columns and splenectomy, on the basis of the results of transplantation involving 52 ABO-incompatible grafts from living related donors.¹⁵ Moreover, 20 percent of patients awaiting transplantation who are undergoing dialysis have a low titer of anti-red-cell antibodies.¹⁶ Another entirely different approach that could be considered is kidney exchanges between pairs of spouses to achieve ABO compatibility.

The risk of donor mortality (currently 0.03 percent¹⁷) and the possibility of coercion of donors are the major issues of concern with spousal donors.¹⁸ However, once the procedure is explained and the willingness of a

spouse to become a donor is established, the use of spousal transplants should be as justifiable as the use of transplants from any other living related donor.

Nevertheless, efforts to increase the availability of cadaveric organs, ultimately the ideal source, should not diminish. The results of the transplantation of cadaveric kidneys, even those obtained from donors whose hearts had stopped beating, should be similar to those for grafts from living unrelated donors once the problem of potential damage to cadaveric organs by hyperfiltration is addressed.

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REFERENCES

1. Pirsch JD, Sollinger HW, Kalayoglu M, et al. Living-unrelated renal transplantation: results in 40 patients. *Am J Kidney Dis* 1988;12:499-503.
2. Park K, Kim Y-S, Lee E-M, Lee H-Y, Han D-S. Single-center experience of unrelated living-donor renal transplantation in the cyclosporine era. In: Terasaki PI, Cecka JM, eds. *Clinical transplants 1992*. Los Angeles: UCLA Tissue Typing Laboratory, 1993:249-56.
3. Yoon Y-S, Jin DC, Yang CW, et al. The effect of HLA mismatching on graft survival in living-donor kidney transplants: Catholic Medical Center, 1984 to 1993. In: Terasaki PI, Cecka JM, eds. *Clinical transplants 1993*. Los Angeles: UCLA Tissue Typing Laboratory, 1994:275-83.
4. Najarian JS, Gillingham KJ, Sutherland DE, Reinsmoen NL, Payne WD, Matas AJ. The impact of the quality of initial graft function on cadaver kidney transplants. *Transplantation* 1994;57:812-6.
5. Wyner LM, Novick AC, Strem SB, Hodge EE. Improved success of living unrelated renal transplantation with cyclosporine immunosuppression. *J Urol* 1993;149:706-8.
6. Haberal M, Gulay H, Tokyay R, Oner Z, Enunlu T, Bilgin N. Living unrelated donor kidney transplantation between spouses. *World J Surg* 1992;16:1183-7.
7. Sesso R, Klag MJ, Ancaio MS, et al. Kidney transplantation from living unrelated donors. *Ann Intern Med* 1992;117:983-9.
8. Geffner SR, D'Alessandro AM, Kalayoglu M, et al. Living-unrelated renal donor transplantation: the UNOS experience, 1987-1991. In: Terasaki PI, Cecka JM, eds. *Clinical transplants 1994*. Los Angeles: UCLA Tissue Typing Laboratory, 1995:197-201.
9. Cecka JM, Terasaki PI. The UNOS Scientific Renal Transplant Registry. In: Terasaki PI, Cecka JM, eds. *Clinical transplants 1993*. Los Angeles: UCLA Tissue Typing Laboratory, 1994:1-18.
10. Terasaki PI, Koyama H, Cecka JM, Gjertson DW. The hyperfiltration hypothesis in human renal transplantation. *Transplantation* 1994;57:1450-4.
11. Stata statistical software, release 4.0. Vol. 2. College Station, Tex.: Stata Corporation, 1995:506.
12. Gjertson DW. Multifactorial analysis of renal transplants reported to the United Network for Organ Sharing Registry. In: Terasaki PI, Cecka JM, eds. *Clinical transplants 1992*. Los Angeles: UCLA Tissue Typing Laboratory, 1993:299-317.
13. Heemann UW, Azuma H, Tullius SG, Mackenzie H, Brenner BM, Tilney NL. The contribution of reduced functioning mass to chronic kidney allograft dysfunction in rats. *Transplantation* 1994;58:1317-22.
14. Riehle RA Jr, Steckler R, Naslund EB, Riggio R, Cheigh J, Stubenbord W. Selection criteria for the evaluation of living related renal donors. *J Urol* 1990;144:845-8.
15. Tanabe K, Takahashi K, Sonda K, et al. ABO-incompatible living kidney donor transplantation: results and immunological aspects. *Transplant Proc* 1995;27:1020-3.
16. Cecka JM, Breidenthal SE, Terasaki PI. Low anti-A and anti-B titers in some type O patients may permit renal transplantation across the ABO barrier. *Transplant Proc* 1987;19:4507-10.
17. Jones J, Payne WD, Matas AJ. The living donor — risks, benefits and related concerns. *Transplant Rev* 1993;7:115-28.
18. Simmons RG. Long-term reactions of renal recipients and donors. In: Levy NB, ed. *Psychonephrology 2: psychological problems in kidney failure and their treatment*. New York: Plenum Press, 1983:275-87.