Living Unrelated Renal Transplantation: Progress and Potential

MOWAFFAQ R. SAID and JOHN J. CURTIS
Division of Nephrology, University of Alabama at Birmingham, Birmingham, Alabama.

Abstract. Transplant centers are turning to emotionally related or living unrelated kidney donors more often than in the past. Such donors are a benefit to the patient with end-stage renal disease, yet concern about their use persists. In the United States, the use of related donors has been well established in most centers. Nonetheless, there had been a reluctance to use nonrelatives that only recently has started to change. Most physicians agree that kidney transplant results are improved with living unrelated donor utilization. The transplant community needs to be watchful of the living unrelated donor operation. Both the welfare of the donor and the possibility of a “slippery slope” toward kidney bartering are considerations that need careful monitoring.

Early in the history of kidney transplantation, the use of kidneys from donors other than parents, siblings, or children (living unrelated donors [LURD]) was common (1). Both the success of cadaveric transplantation and the initial negative assessment of results of such LURD led most groups to abandon the unrelated donor except for rare circumstances (2). Moreover, the emergence of long-term patient survival on chronic dialysis lessened the “life and death” emergency nature of early kidney transplantation. Thus, transplant registry records of the 1970s and 1980s record few LURD.

In the last half of the 1990s, however, there has been an impressive revival of LURD transplantation. The United States Renal Data System (USRDS) lists a greater than 100% increase of such transplants from 1994 until 1996. During the same time frame, the cadaveric transplant rate barely changed. As with most dramatic changes in transplantation, there are pros and cons to LURD transplantation. This report will attempt to present these pros and cons, but the reader should be aware that the author is (cautiously) in favor of these types of transplant operations. Changes in transplantation patient survival rates, dialysis patient survival rates, operative procedures, and long-term follow-up along with cadaveric organ shortages are in flux (although the shortage has been steadily getting worse). Such changes can alter the view of LURD transplantation as dramatically as it has changed from the 1980s to the 1990s. Xenotransplantation could, more than any other imponderable, change everything.

Pros

The enhanced medical benefit to patients who have developed end-stage renal disease (ESRD) is the number one advantage to be realized by use of LURD. Availability of LURD to ESRD patients results in patients avoiding or spending less time on dialysis. Long-term survival of ESRD patients is better with kidney transplantation (3). Moreover, the length of time on dialysis prior to transplantation appears to negatively affect survival of patients (4).

Although controlled trials directly comparing dialysis to transplantation have not been done, recent reports using registry data make a compelling case that any form of transplantation provides superior patient survival (5). Knowledge of the improved success rates of transplantation has drawn more ESRD patients to be evaluated and placed on transplant waiting lists. These “wait-listed” patients have a survival advantage over patients not on such waiting lists. The existence of this selected group of patients in large numbers who (unfortunately) remain on waiting lists for considerable time periods occurred as the USRDS matured in its data collection and analysis. The combination of these two events has answered a question about survival that today generates little debate. Transplanted patients have a lower rate of death than patients who are not transplanted. Moreover, LURD transplanted patients have survival rates that are in the best category of transplant results (6).

Improved survival of the patient with ESRD is the foremost argument for LURD transplantation. Unexpectedly, allograft survival rates are another favorable justification for LURD (7). Since the HLA antigen matching of unrelated donors might not be expected to be optimum (indeed, it is poorer than cadaveric transplantation), it was suspected that allograft outcome would be no greater than that seen in cadaveric transplantation. This has not been the case. Almost all reports suggest that such poorly matched donors have excellent allograft survival rates (8–11). The Brazilian Transplantation Registry, which was among the first organizations (12) to call attention to this
“surprisingly” good outcome, has recently updated data with 10-year follow-up (13). The survival advantage holds over the long term. The advantage cannot be explained by better immunosuppressive drugs, because it was reported by the Brazil group and other large single centers long before the introduction of the newer drugs. Terasaki et al. (7) (long an advocate of the influence of HLA matching on allograft survival rates) published a landmark report confirming the finding of excellent allograft survival despite poor HLA matching. Opelz (14), however, suggested from his data that the best matched of the unrelated donors do better than the less well matched. He contends that the surprise finding of such good results for LURD should not be used to minimize the importance of HLA matching.

There are a number of speculations to explain the superior allograft survival rates in LURD transplantation. None of the theories, however, is yet supported with overwhelming scientific facts. For example, it has been suggested that medical compliance might be greater among patients whose spouse donated their kidney (15). It is also possible that recipients who have the type of family or emotionally related friends that would give a kidney might be more responsible patients. Thus, positive patient selection factors could be at work. Others have pointed to the problems of death in cadaveric donors (16). The intense release of hormonal substances during the last minutes of life may dispose the allograft to inferior results. More obvious (but less accepted by many investigators) is the difficulty of transporting such cadaveric kidneys and the problems of long cold ischemia times (17). Whatever the reason, LURD outperform cadaveric kidneys in both the short- and long-term.

As this survival advantage becomes accepted, transplant programs have expanded their donor pool to include zero-haplotype HLA living related donors (18)—a group that in the past was excluded because they were expected to do no better than cadaveric recipients. Figure 1 shows the increase in use of LURD and zero-haplotype LRD at the University of Alabama at Birmingham. Figure 2 shows the allograft survival rates of allografts from these types of donors. Similar to reports in the literature from other centers, our results compare favorably to traditional LRD results and demonstrate a rapid increase in such donors.

For the ESRD patient, then, both patient survival and allograft survival rates are favorable justifications to advocate LURD transplantation. There are, however, other, less direct but substantial benefits. Each LURD transplant performed means that a scarce cadaveric kidney can be used for another ESRD patient. Thus, more patients benefit from kidney transplantation. In addition to improved survival for the patients, transplantation is acknowledged to provide a better quality of life for ESRD patients. It is a far less costly form of therapy than chronic dialysis. Expanded LURD transplantation has positive benefits for society—it can help diminish the major problems of cadaveric organ shortages and reduce the cost of ESRD treatment (19).

LURD transplant operations, like LRD transplants, are less labor-intensive and are performed under less “emergency-like” conditions. They can be scheduled at a time when the operating team is fresh and perfectly staffed. Such operations are elective and time is available to ensure that the recipient is in top medical condition for surgery. Cadaveric organ harvesting is one of the most difficult aspects of delivering organ transplantation on a large scale. Considerable surgical manpower, institutional support, community support, educational programs, etc., are needed to secure large numbers of cadaveric organs. The amount of labor is underestimated by many and, in my opinion, is a major factor explaining the variable rates of transplantation seen across the country and the world. The use of LURD and LRD is less labor intensive (which can be

**Figure 1.** The numbers of transplants performed from unrelated (mostly spouses) and zero-haplotype donors have increased in our program as well as nationally. ■, friends; ●, spouse and other; □, zero-haplotype.
considered both a pro and a con for such transplantation). Obtaining cadaveric organs is the most difficult aspect of kidney transplantation. It is neither glamorous nor prestigious and requires the work and cooperation of a vast number of people that includes the general public.

Cons
Although the ESRD patient is the beneficiary of LURD transplantation, the donor is the main concern of those who question such transplantation. As with LRD, only people who are in perfect health are considered for unrelated donor surgery. To propose major surgery for healthy people is contrary to most medical recommendations. Surgery in which the best possible outcome is that the person will not be worse off than before the surgery is a departure from most patient-directed interventions. Major surgery is usually performed for correctable pathologic conditions of the individual. Thus, the same concern is present for the unrelated donor as has been present for related donors for years (20).

Investigators have reported several examples of related donors who have developed ESRD themselves, years after donation (21–23). Because such outcomes are not very pleasant, it is likely that they are underreported. Currently, there is no good database (in the United States) to determine the exact number of patients who served as donors and are now suffering from ESRD themselves. On the other hand, it is likely that some donors who progressed to renal failure had preexisting renal problems that were not uncovered before the operation (24). Other donors would be expected to develop diseases such as diabetes and hypertension leading to ESRD regardless of their donor status.

Although the reported risks for such problems for the donor are rare (25,26), the quality of the data in these reassuring reports is not as firm as it might be. An excellent study (because it was the first to include a control group of family members who were evaluated but not selected as donors) published by Williams et al. (27) found no major medical problems for the donors. This study, however, had only 38 study patients and 17 controls. With such low study numbers, important differences in the groups could have been easily missed. There is no registry for donors, and follow-up in this country has been neither uniform nor complete. Follow-up in other countries, however, has been better and is reassuring. In Sweden, being a donor has been reported to be a favorable risk factor for longer life (28)?

On the basis of animal experiments, there may be a limited amount of renal tissue that can be removed before a chain of events is set in motion that will result in the inevitable destruction of the remaining tissue (29,30). Although the 50% removal of tissues in donors (related and unrelated) has not yet been implicated as a certain cause of ESRD, Hakim et al. (31) have suggested that such donors may be at risk for increased rates of proteinuria and hypertension. Although long-term follow-up of donors is desirable, the means for such follow-up are not well established. On the whole, however, most of the published data suggest that risks to donors are quite rare. On the plus side, donors often have unexpected medical problems found during their evaluation, and not a few are indeed lucky that they had a medical evaluation (32). Moreover, donors can have psychological benefits from the act of donation (33).

A recent survey of donors (including LURD) noted several points that the transplant community needs to consider (34).

---

**Figure 2.** Five-year allograft survival rates (1984 to 1997) for unrelated donor transplants is at least as good as that for related donors, and both are better than cadaver donors. , cadaveric donor (n = 2359); ■, living related donor (n = 924); ▲, living unrelated donor (n = 62).
Thirty-four percent of the donors felt that the degree of pain associated with the donation was more than they had anticipated. Thirty-one percent would have appreciated more information in preparation for donation. Fifteen percent believed that donation affected their health negatively. For most donors (77%), there were negative financial consequences of donation. Thirteen percent reported emotional pressure to donate and half of these felt the pressure came from the transplant team. Despite the percentages quoted above, this survey—in its entirety—was a very favorable report. The overwhelming majority of donors were highly satisfied with the operation, had few criticisms, and would recommend donation. Yet the negative comments need to be considered in this discussion.

As noted above, the fact that LURD ease the workload on transplant centers can be both a pro and a con. Some centers have demonstrated a decrease in other types of transplants as the number of LURD increase (35). It is possible that expanded LURD operations might have a negative effect on the cadaveric programs that have been so painstakingly developed in transplant units in this country. This would, of course, be a disaster for ESRD patients in general. Thus far, in this country there has been no evidence of such a development.

More worrisome is the conceivable move toward a nonaltruistic form of transplantation—kidney bartering. The major demand and supply imbalance has not gone unrecognized for those who would turn the altruistic and voluntary cadaveric or living related transplant programs into a bartering system to make a profit. The chilling aspect of body parts allegedly being sold in New York City should be enough to put the transplant community on high alert. LURD transplants may have an advantage over LURD in that the assumption that the act is altruistic may be less often wrong among blood relatives. LURD transplantation, on the other hand, may lead to a so-called “slippery slope” (36) toward less than altruistic motives. Evidence of this fear has recently been documented in the lay press.

In the United States, competition to perform large numbers of transplants could lead centers to “push the envelope.” The rapid adoption of non-heart beating donors, so-called marginal donors, hepatitis C-positive donors, etc., seems to be fueled not only by the growing waiting lists but also by desires for centers to “increase their numbers.” Competition is not undesirable in itself, but the conditions in the United States are (in my view) not as cautious in adopting change as they might be. The many positives in increasing transplantation rates (a better therapy at a lower cost) make a cautious, guarded, and slow adoption of change a competitive disadvantage.

LURD transplantation, then, has the possibility of tarnishing the image of transplantation, which could in turn harm all ESRD patients. The altruistic cadaveric harvesting system is dependent on public attitudes and can be easily undermined. Fear of nonvoluntary donation or kidney bartering could in the end lower the rate of transplantation. Rapid expansion of donors from all sources without critical self-examination of motives can lead the transplant community (which currently is held in high public esteem) into dangerous territory. There continues to be a need for the transplant community to be conservative and focused on what is best for the ESRD patient and not necessarily what is best to become the favored program of the medical payers.

Thus far, the fears of LURD having a negative effect on transplant programs have not materialized. For years, the United States has been the leading proponent of LRD transplantation. Europe, Australia, and Canada have recently increased their rates of LRD transplantation. The move to LURD in this country is also a leading position. Nonetheless, some of the best discussions regarding the ethics of both LRD and LURD have come from Europe. A recent publication by Darr et al. (37) detailing the work of a Munich committee (Interdisciplinary Arbeitsgruppe Lebensspende) is a landmark statement on the issue from Germany.

This committee clearly separates the ethics of donation and genetic relationships. Genes do not guarantee the correctness of behavior. There can be unethical donation from relatives as well as nonrelatives. The need for altruistic and noncoerced donation is emphasized. Genetic ties do not determine what is and is not ethical. The well thought out ethical position of this group also includes a detailed plan (The Munich Protocol) of evaluation of LRD that includes nontransplant team involvement. The implication is that the actual transplant team needs outside involvement in such decision making.

At least two other countries have adopted a formal review process for LURD, perhaps motivated by different histories. This pertains to the more difficult nonspouse (“friends”) type of LURD. In India, international kidney bartering had become infamous. A new system that requires approval of LURD by a committee with nontransplant medical personnel has brought the commercial scandal of India nearly to a halt and at the same time increased the rate of LRD transplantation in that country (38). In England, a country with a lower rate of living donors than the United States, an extensive evaluation system that also involves medical personnel that are not part of the “transplant team” operates smoothly, and such transplantation procedures are increasing (John Freehally, consultant nephrologist, Leicester General Hospital, Department of Nephrology, Leicester, England, personal communication).

In the United States, the cooperation (and trust) of government and medicine is not as well established as in some other countries, but it is possible that nonspouse, emotionally related transplantation is an area in which some form of monitoring is required. A nongovernment agency with highly developed database skills and respect from the transplant community such as the United Network of Organ Sharing (UNOS) might be the proper organization to consider this mission. UNOS has a strong track record of fairness, understanding of complex issues, devotion to justice, maximum utility of organs, and freedom from even a hint of corruption. It, like Caesar’s wife, is beyond reproach. The current situation, however, in which LURD decisions are made with the transplant team and individuals involved is, in my view, more likely to be well done than one that involves either the legal or political systems of this country. Unless, of course, kidney bartering becomes a problem that neither the medical profession nor UNOS or the
professional kidney transplant medical societies is able to handle, it would be better to keep the current system.

References