Living donor renal transplantation: recent developments and perspectives

Seema Baid-Agrawal and Ulrich A Frei*

SUMMARY

Renal transplantation is the optimal treatment for patients of all ages with end-stage renal disease. Life expectancy of the population in general is increasing consistently, as is the age of the dialysis population. Consequently, the average ages of kidney donors and recipients are rising. The combination of a growing number of patients with end-stage renal disease and a shortage of organs poses a significant challenge to the transplant community. Donor shortage is associated with unfavorable consequences (e.g. prolonged waiting time, and compromised graft and patient survival). As such, multidirectional efforts are required to expand the donor pool. Increasing the frequency of living donation seems to be an efficient solution. Living donation is associated with superior results for the recipient, and relatively benign long-term outcomes for donors. Reluctance to use organs from living donors whose eligibility was previously considered marginal (e.g. elderly donors) is declining. Although increased donor age is associated with reduced graft survival rates, this should not preclude use of older living donors; transplantation is definitely superior to remaining on dialysis. Thorough, standardized evaluation and careful screening for premorbid conditions in both elderly donors and elderly recipients are essential. Here, we present various options for expanding the living donor pool, with emphasis on the utilization of elderly living donors and transplantation in elderly recipients.

KEYWORDS elderly donor, elderly recipient, expanded criteria donor, living donor, renal transplantation

REVIEW CRITERIA

We focused our literature search on the PubMed and MEDLINE databases, and used the following search terms in different combinations: "renal transplantation", "living related", "living unrelated", "living donors", "elderly donors", "elderly recipients", "expanded criteria donors", "preemptive transplantation", "paired exchanges", "altruistic donation", "ABO-incompatible transplantation" and "HLA-incompatible transplantation". We concentrated on English-language articles and abstracts that have appeared in nephrology and transplantation publications in the past 5 years. We also searched article bibliographies for other relevant papers.

S Baid-Agrawal is a staff nephrologist, and UA Frei is Chief, in the Department of Nephrology and Medical Intensive Care, Campus Virchow-Klinikum, Charité Universitaetsmedizin Berlin, Germany.

Correspondence

*Department of Nephrology and Medical Intensive Care, Campus Virchow-Klinikum, Charité Universitaetsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
ulrich.frei@charite.de

Received 17 August 2005 **Accepted** 31 October 2006

www.nature.com/clinicalpractice
doi:10.1038/ncpneph0383

INTRODUCTION

The first successful living donor renal transplant, performed in Boston in 1954 between identical twins, is a notable landmark in medical history. Remarkable medical and surgical advances in renal transplantation over the subsequent half century have advanced this modality so that it is now the optimal treatment for end-stage renal disease (ESRD). Renal transplantation improves patient survival and quality of life; it is also cost-effective when compared with hemodialysis and peritoneal dialysis.[1] The long-term mortality rates among transplant recipients are 49–82% lower than those of patients on transplant waiting lists (depending on comorbidities).[1] The survival and economic benefits of transplantation are evident across all age-groups.

The ESRD population is growing worldwide and has doubled in the Western world during the past decade.[2] The elderly comprise the most rapidly expanding segment of the ESRD population.[3] Consequently, the number of patients on transplant waiting lists has increased steadily, but there has been no concomitant increase in organ supply. This increasing disparity has resulted in a serious shortage of kidneys, leading to prolonged periods of dialysis and increased death rates for patients on waiting lists.[1] Prolonged dialysis is associated with poor post-transplantation graft and patient survival.[4–6]

Increasing the number of donor kidneys is a major contemporary challenge. Recent evidence indicates that only 42% of potential deceased donors become actual donors in the US, and even if the organs of all potential brain-dead donors were utilized, the supply of kidneys would still be insufficient to meet the escalating demand.[7] One potential solution to expand the donor pool is to increase the number of living donors. Transplantation from both living related and living unrelated donors is now widely accepted as a highly effective method of treating ESRD in selected recipients. Besides combating the increasing gap between organ supply and demand, living donation is associated with superior

Box 1 Potential benefits and risks of living kidney donation.

Potential benefits

- Improved graft and patient survival, primarily due to superior organ quality, better HLA matching, shorter cold ischemia time, negation of negative donor-related factors (e.g. brain death, cardiovascular instability, use of vasopressins), short waiting time on dialysis, and feasibility of pre-emptive transplantation
- Facilitation of pre-emptive transplantation, which allows avoidance of dialysis-related complications, provides optimal medical and psychological condition of the recipient at the time of surgery, reduces risk of acute rejection, and improves graft and patient survival
- Expansion of total donor pool

Potential risks (to the donor)

- Perioperative morbidity and mortality
- Renal dysfunction in the long-term
- Financial penalties from loss of work-time

long-term outcomes when compared with renal transplants using organs from deceased donors. A disadvantage of living donation is that it requires a major surgical procedure with associated risks of morbidity and mortality. Living with a single kidney can also confer long-term risks. Consideration of living donation, therefore, involves weighing the benefits to the recipient against the risks to the donor.

LIVING VERSUS DECEASED DONOR TRANSPLANTS: BENEFITS AND RISKS

Over the past few years, the benefits of living donor transplantation—compared with all forms of deceased donor transplantation—have been well recognized (Box 1). Use of living donors is associated with better graft and patient survival rates and a reduction in the time patients spend on dialysis. The half-life of renal allografts from living donors is 21.6 years, compared with 13.8 years for deceased donor organs.[8]

The availability of a living donor also facilitates pre-emptive transplantation (i.e. transplantation prior to initiation of dialysis). The advantages of using a living donor (outlined above) are more pronounced in pre-emptively transplanted patients. Pre-emptive transplantation negates dialysis-related complications, and is associated with reduced risk of acute rejection as well as better allograft and patient survival.[5,9–11] Furthermore, recipients are generally in better medical and psychological condition at the time of pre-emptive transplantation than following dialysis. In an analysis of data from the United States Renal Data System (USRDS) database, Meier-Kriesche and Kaplan showed that 10-year graft survival was 78% for patients receiving pre-emptive transplants from living donors versus 48% for those who underwent transplantation after 24 months on dialysis.[5] Living donor transplantation after recipients had been on dialysis for more than 24 months resulted in the same graft survival rates as transplants from deceased donors performed within 6 months of joining waiting lists.[5] This phenomenon might account for a large proportion of the advantage of living donor transplantation over deceased donor transplantation. Other reasons for improved outcome could include superior organ quality, shorter cold ischemia time, negation of donor-related factors (e.g. brain death, cardiovascular instability, use of vasopressins) and a better human leukocyte antigen (HLA) match.[12] Excellent outcomes have been observed, even in cases of unrelated living donation in which there is poor matching for HLA antigens.[13,14]

The fundamental principle of 'first, do no harm' to the donors must be the primary consideration when contemplating living donation. Donors undergo a major operation with potential risks of perioperative morbidity and mortality, and renal dysfunction in the long-term. Perioperative mortality for living kidney donors (donation by both open and laparoscopic methods) is 0.03%.[15] Despite this relatively low mortality rate, there is a need for accurate ongoing reporting of donor operative outcomes. Existing evidence, mainly from retrospective surveys, indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy.[16–18] Most donors had normal renal function 20–37 years after donation.[18] Rates of proteinuria and hypertension were similar to those of the age-matched general population. Nevertheless, five (1%) donors developed ESRD and three others had abnormal renal function.[18] Ellison and colleagues identified 56 living kidney donors in the Organ Procurement and Transplantation Network database who were themselves listed for a kidney transplant.[19] ESRD affected 0.04% of donors, a rate comparable to that of the general US population. To ensure their safety, all donors must undergo a complete and

standardized predonation medical and psychosocial evaluation, receive appropriate instruction on providing informed consent, and be capable of understanding the information presented such that a voluntary decision to donate organs can be made.[20]

STRATEGIES TO EXPAND THE LIVING DONOR POOL

Enhanced public and provider awareness of living donor kidney transplantation has promoted increases of 68% and 1,000%, respectively, in the numbers of living related and unrelated donors in the US over the past decade.[21] The number of living donors has actually surpassed that of deceased donors in some countries, including the US (Figure 1). The advent of laparoscopic donor nephrectomy has further propelled this change in practice. Despite this improvement, demand for organs still surpasses supply. Further increasing the number of living donors will require both innovative approaches and continued public education. Various strategies that are currently used to expand the living donor pool are summarized in Box 2.

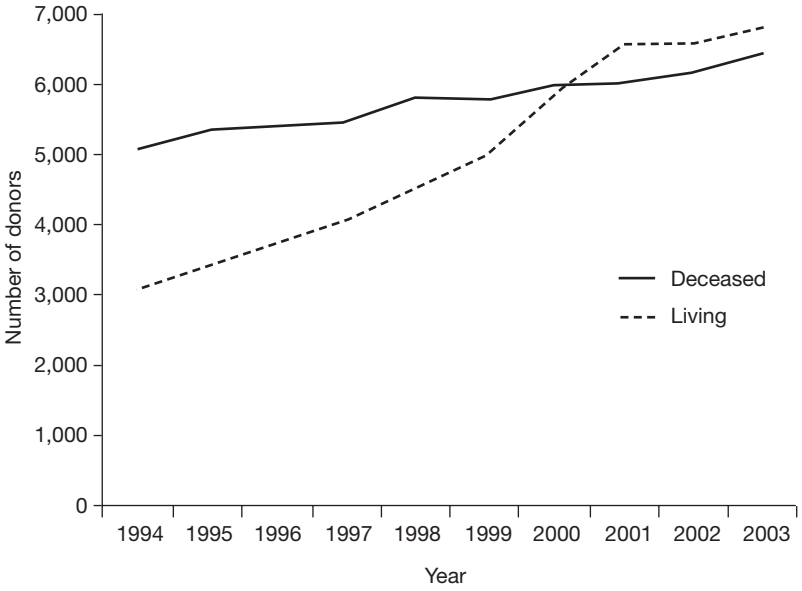

Figure 1 Number of living and deceased kidney donors in the US from 1994 to 2003. Data from the 2004 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients Annual Report 1994–2003 (http://www.optn.org/ar2004/). These data have been supplied by the United Network for Organ Sharing (UNOS) and the University Renal Research and Education Association (URREA) under contract with the Department of Health and Human Services (HHS). The authors alone are responsible for reporting and interpreting these data; the views expressed herein are those of the authors and not necessarily those of the US Government.

Genetically unrelated donors

In the past, 'living donation' meant donation by a sibling, parent or, sometimes, a child of the recipient (genetically related). Now, 'living donation' encompasses donation by a spouse, friend, acquaintance ('emotionally related') or even a complete stranger ('altruistic' or 'nondirected'). New immunosuppressive agents have permitted expansion of the living donor pool to include such emotionally related and nondirected donations. Data indicate that outcomes of living donor kidney transplants between genetically unrelated donors and recipients are superior to those using deceased organs with closer HLA matching (Figure 2).[13] Further, the results of unrelated living donor transplantation are similar to those of living donor transplantation matched for one haplotype—a better outcome is achieved only by using an HLA-identical kidney.[13,14,22,23] As a result of these findings, interest in living unrelated transplantation has increased and protocols for nondirected living donation have been developed (see below).

Box 2 Strategies to expand the living donor pool.

- Use of genetically unrelated donors such as a spouse, friend or acquaintance (emotionally related donors) or a stranger (altruistic or living nondirected donors [LNDs])
- Paired-donor kidney exchanges, either direct (living-donor–living-donor) exchanges (kidney-paired donation) or indirect (living-donor–deceased-donor) exchanges (list-paired donation)
- Integration of paired exchanges with LND donation, as either domino-paired donation (LND donation plus direct exchanges) or chain-paired donation (LND donation plus direct and indirect exchanges)
- Transplantation across ABO or HLA barriers using desensitization techniques
- Use of expanded-criteria living donors including hypertensive donors, obese donors and elderly donors

Altruistic or nondirected donation

The success of living unrelated transplantation has led transplant physicians to consider the requests of individuals who volunteer as kidney donors but do not specify a recipient. Currently, such donors are dubbed living 'nondirected' (LND) or 'altruistic' donors. LND donation

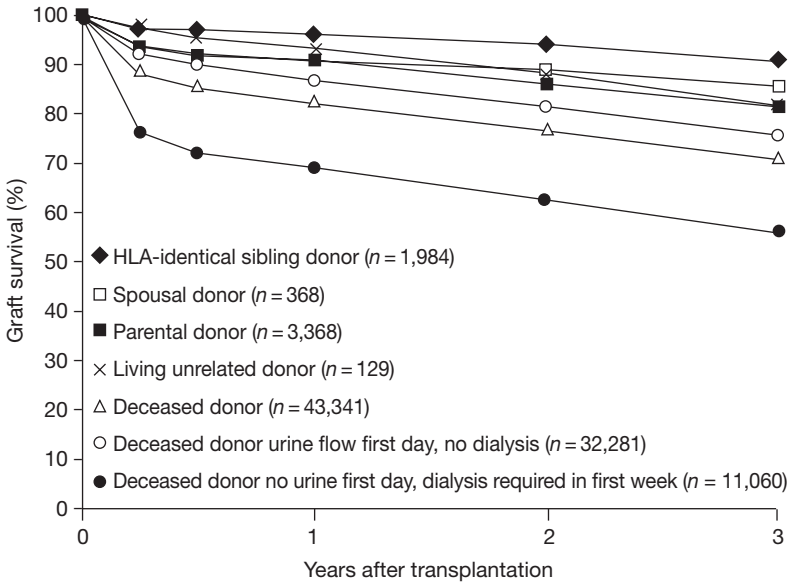

Figure 2 Survival of first kidney grafts. The survival rates of both spousal grafts and grafts from other living unrelated donors were similar to that of grafts from living donors with one haplotype match (parental donors) and superior to that of grafts from deceased donors. The grafts from HLA-identical siblings had the highest survival rates. Abbreviation: HLA, human leukocyte antigen. Permission obtained from Massachusetts Medical Society © Terasaki PI *et al.* (1995) *N Engl J Med* **333:** 333–336.

must be distinguished from directed donation, which involves designation of a donor organ for a specific individual. Any person who is competent, willing to donate, free of coercion, and found to be medically and psychosocially suitable, can be a living kidney donor in the US.[24] In most other regions of the world, acceptance of such unconventional LND donors, however, has not occurred because of the difficult legal and ethical issues raised by this practice. Transplant centers that accept donors in this category should document an informed consent process that details donor risks and ensures donor safety. Motives for donation should also be established, with care taken to avoid donors who intend to remedy a psychological disorder via donation. Benefits to both donor and recipient must outweigh the risks.

At the University of Minnesota, a nondirected protocol has resulted in 23 successful donations.[25] Such a program is, however, highly labor-intensive, as underscored by the fact that telephone screening interviews of the 362 potential LND donors led to only 53 comprehensive evaluations at the center and 23 transplants. Staff at this center emphasize the importance of a highly dedicated donor management team and the need for additional time and resources, given the number of practical, logistical and ethical issues inherent in LND donation.

Paired-donor kidney exchanges

Over the past few years, paired-donor kidney exchange programs have generated considerable international interest. A paired exchange program between two living-donor–recipient pairs was developed in Korea by Park and co-workers as a therapeutic option for ESRD patients whose only available living kidney donor is willing to donate, but is ABO blood-type incompatible or HLA incompatible.[26,27] At the time of their latest report, 101 exchanges had been performed. Five-year graft and patient survival were comparable to those for living unrelated donor transplants.[28] Exchange programs increase the likelihood of resolving ABO and crossmatch incompatibility without exposing recipients to the risks associated with additional immunosuppression; which is necessary for desensitization programs. Paired-donor kidney exchanges might prevent loss of a significant number of suitable living kidney donors, and thereby have a positive impact on the current acute shortage of organs for transplantation. These programs are now classified as either direct or indirect.[29]

Direct (living-donor–living-donor) exchanges (or kidney-paired donation)

In a direct paired exchange program, kidneys from living ABO-incompatible or lymphocyte-crossmatch-incompatible donors are available via arrangement between two living-donor–recipient pairs. Swapping donors makes possible two compatible living donor kidney transplants. In most instances there are no ethical obstacles to direct exchange, as the net gain for the two pairs does not differ from that of direct living donation and the exchange occurs on the basis of equality. There is no negative impact on the deceased donor list.

Despite the increasing popularity of direct exchanges, these transplantations are currently being performed at only a few centers, with matches identified through local or regional patient databases. To expand the opportunity for such exchanges, it is crucial to determine the most cost-effective method, optimal allocation priorities, and algorithms for matching patients and donors at the outset. Various computerized

models using simulated pools of incompatible donor–recipient pairs have been designed to facilitate identification of the maximum number of compatible donor–recipient pairs from registries of incompatible pairs.[30–32] It has been suggested that, using such a mathematically optimized matching algorithm, the nationwide pool of incompatible patients (predicted to be 2,500–4,000 registrants per year in the US) could achieve a match rate of 47%.[30]

Indirect (living-donor–deceased-donor) exchanges (or list-paired donation)

The exchange program between living-donor–recipient pairs has been further evolved by the United Network for Organ Sharing Region 1 to include living-donor–deceased-donor exchange.[29] This system helps patients who have an incompatible living donor available but are unable to participate in a living donor paired exchange. The exchange involves the donor of an incompatible pair giving a kidney to a patient at the top of the deceased donor waiting list, after which the living donor's original intended recipient is given 'priority points' so that they will receive the next ABO-identical or O type (T-cell crossmatch negative) deceased donor kidney available within the region; the original intended recipient does not take priority over candidates who are zero mismatch or sensitized, or over children. Offering the exchange-participant priority for an O blood type kidney seriously disadvantages O type candidates on the already long deceased donor waiting list. As such, indirect exchanges have been challenged on ethical grounds and have not been globally acclaimed.

Integration of paired exchanges with living nondirected donation

Recently, a new type of paired donation—'domino-paired donation'—has been proposed to improve the qualitative and quantitative benefit of each LND donation.[33] In this strategy, the LND donor is allocated to a pool of direct-exchange pairs. First, the LND donor's kidney is matched to a recipient who has a willing but incompatible donor. The recipient's incompatible donor can, in turn, agree to give a kidney to the next compatible patient on the transplant waiting list, generating a 'domino' effect. In this way, two living donor kidney transplantations result, multiplying the impact of the donor's gift. Furthermore, integrating direct and nondirect exchanges with LND donation (through chain exchanges) has been shown to increase the number of individuals who receive a transplant without creating any further adverse effect on O blood type candidates on the deceased donor waiting list.[34]

Transplantation across ABO or HLA barriers

ABO blood type incompatibility or T-cell crossmatch reactivity between donor organs and recipients would result in an accelerated rejection of the allograft. Historically, therefore, these factors have been considered as absolute contraindications to transplantation.[35–37] In most centers, between 30% and 40% of all otherwise-acceptable living donors are presently rejected because of ABO incompatibility. Moreover, approximately 20–30% of patients on transplant waiting lists in the US are highly sensitized against HLA antigens and cannot find a compatible living donor. Until recently, therefore, ABO and HLA incompatibility have been two of the greatest barriers to optimal utilization of kidneys from living donors.

Performing the transplant despite incompatibility is another recent exciting advance for ABO-incompatible or HLA-incompatible living-donor–recipient pairs, besides paired-donor kidney exchanges. Successful desensitization of some of these patients has been possible, allowing living donor transplantation or deceased donor transplantation across these biological barriers.[36–45] The overall goal of desensitization is to reduce antibodies against donor ABO or HLA before and after transplantation. Two desensitization protocols have shown great promise in accomplishing this goal: first, plasmapheresis or extracorporeal immunoadsorption, and second, intravenous immunoglobulin (IVIG), both in conjunction with maintenance immunosuppression using mycophenolate mofetil and tacrolimus with or without steroids.

IVIG is used in high doses (2 g/kg body weight) for patients awaiting either a deceased or living donor transplantation, and in low doses (cytomegalovirus hyperimmune globulin [CMVIG] 100 mg/kg body weight) in combination with plasmapheresis for patients with living donors only.[37] IVIG has well-recognized but poorly understood immunomodulatory effects. Rituximab, a high affinity CD20-specific monoclonal antibody, has

become an important (off-label) adjunct in desensitization protocols. This agent is a rational choice for desensitization, as it attenuates alloimmune responses by abrogating B-cell-mediated events.

The persistence or reappearance of antibodies, resulting in antibody-mediated rejection (AMR) of the graft, are potential risks of transplantation across ABO or HLA barriers. The risk of AMR is highest during the first 10 days following transplantation. Acute AMR should be diagnosed on the basis of allograft dysfunction, rising antibody titers and the presence of deposits of the complement component C4d in peritubular capillaries.[35,37] Recently, the identification of C4d deposits was found to be an important indicator of AMR in HLA-incompatible grafts; identification did not, however, correlate with injury in most ABO-incompatible grafts.[46] Treatment of acute AMR includes lowering antibody levels with pulse steroids, plasmapheresis plus CMVIG for mild cases, and rituximab and/or urgent splenectomy for severe cases.[37]

ABO-incompatible transplantation

ABO-incompatible transplantation has become relatively common in Japan over the past 20 years because of the very limited number of deceased donors in that country. Excellent outcomes at 9 years, comparable to those following ABO-compatible transplantation, were reported in a large Japanese series of 441 ABO-incompatible living donor renal transplants with splenectomy.[43] Splenectomy, however, remains a major impediment to wider acceptance of ABO-incompatible transplantation. The need for splenectomy has recently been questioned, as substitution of splenectomy with rituximab has been associated with good results.[44,45] Extending their previous observations, Tyden *et al.* have reported successful ABO-incompatible transplantation without splenectomy in 21 patients using antigen-specific immunoadsorption, one dose each of rituximab and low-dose IVIG (0.5 g/kg body weight), and a conventional triple-drug immunosuppressive protocol.[44] These results have been reproduced by Sonnenday *et al.* in six ABO-incompatible recipients.[45]

HLA-incompatible transplantation

Successful desensitization overcoming positive T-cell crossmatches has been achieved by various centers, allowing safe transplantation with good 1-year and 3-year graft survival rates.[37–41] Using the Hopkins protocol of plasmapheresis and low-dose CMVIG, Montgomery and Zachary have successfully transplanted more than 80 sensitized patients, including some with very highly positive baseline crossmatches.[37] Rituximab or splenectomy are reserved for those at highest risk of severe AMR in this protocol. Rituximab has also been used successfully in a series of 14 patients with a positive pretransplantation living donor crossmatch, in conjunction with an intensive regimen including splenectomy and plasmapheresis; 11 patients maintained their grafts for more than 1 year.[41] Such an intensive protocol has also been used to overcome simultaneous HLA and ABO incompatibility in three patients, with excellent short-term outcomes.[42]

ABO-incompatible and HLA-incompatible living donor kidney transplantation have the potential to increase the size of the living donor pool without disadvantaging candidates on the deceased donor waiting list. Nevertheless, these conditioning regimens are relatively expensive and are still associated with unpredictable rates of biological graft loss and potential risks of intensive immunosuppression. It should also be emphasized that long-term outcomes are not yet known. Randomized, controlled clinical trials are needed to establish optimal peri-transplantation management protocols and to confirm their long-term efficacy.

Extending the selection criteria for living donors

The persistent shortage of organs has forced the transplant community to consider newer, more-controversial options. A wider range of potential living donors is being evaluated than ever before, and selection criteria have been extended to include donors who traditionally would not have been considered. Older people and those with mild hypertension and obesity are being accepted as donors more frequently.

Donor hypertension

Hypertension, most often defined as blood pressures above 140/90 mmHg or the need for antihypertensive medications, is one of the most common reasons for excluding donors who are otherwise eligible.[47] The primary concern is that hypertensive donors might have increased postoperative risks of worsening

hypertension and of developing kidney failure. African American donors and those with a family history of hypertension and/or kidney disease are regarded as particularly susceptible.[19] It is unclear whether or not moderately hypertensive white donors are at appreciable risk in the absence of associated kidney disease. Thresholds for defining hypertension have been constantly lowered over the past two decades. Many donors classified as having normal blood pressure 25 years ago would now be categorized as hypertensive and excluded from kidney donation; however, relatively benign donor outcomes have been reported during follow-up of at least 20 years following kidney donation.[16–18]

The Mayo Clinic has implemented a structured program of accepting moderately hypertensive white kidney donors who satisfy other criteria (e.g. >50 years of age, glomerular filtration rate [GFR] >80 ml/min and urinary albumin excretion <30 mg/day).[47] Twenty-four donors have been followed for between 6 and 12 months, and no adverse effects have been detected on blood pressure, GFR or urinary protein excretion. Notwithstanding encouraging short-term results, it should be emphasized that only individuals with moderate hypertension and no other adverse risk factors (e.g. African American race, family history of hypertension and/or renal disease, and glucose intolerance) may be considered for kidney donation.

Donor obesity

Obese donors, previously discouraged from living organ donation, are now being considered under expanded criteria. Obesity (BMI >30 kg/m^2) is associated with health problems (hypertension, proteinuria and diabetes) and has a negative impact on renal function.[20,48,49] Being overweight could, therefore, increase the risk of a donor developing proteinuria and renal disease. Obesity also increases the risk of perioperative infections and death for patients undergoing a variety of surgical procedures. Nonetheless, as pressure to expand the living donor pool has grown, prudently selected obese donors have been used, with relatively good short-term outcomes.[48] Fasting blood sugar and 75 g 2 h oral glucose tolerance tests should be performed on all obese potential donors. Other comorbidities should be evaluated. Weight reduction programs and education about healthy lifestyle should both be included in the plan for donation.[20]

Elderly donors

Reluctance to use organs from elderly donors has decreased with the increase in demand. Until fairly recently, age greater than 55 or 60 years was often considered sufficient grounds to reject a donor organ, as survival of older grafts is inferior to that of kidneys from younger donors. In most large studies of kidney transplant outcomes, deceased donor age greater than 50 or 60 years has been identified as a strong independent predictor of poorer graft survival.[50–53] The use of kidneys from older donors is associated with increased risk of delayed graft function, acute rejection, chronic allograft nephropathy, increased baseline creatinine and, consequently, increased rates of early and late allograft failure. It is worrying that donor age has recently been identified as a significant risk factor for patient death with functioning graft.[54] The authors of that study speculated that poor function of the aged graft might lead to hypertension and an increased incidence of cardiovascular events.

Concerns regarding the effects of older donor age on deceased donor renal transplant outcome have influenced the assessment of potential living donors at many centers. It is not uncommon for elderly individuals to be discouraged from donation in favor of a younger living donor or placement of the intended recipient on the waiting list for a deceased donor organ. The influence of donor age on the outcome of living donor kidney transplantation is, however, unconfirmed. Both equivalent, as well as reduced, graft survival (as compared with transplantation from younger donors) have been reported.

Kumar and co-workers retrospectively compared the long-term outcomes of 112 recipients of kidneys from elderly (>55 years) living related donors with 87 recipients who had younger donors (<45 years).[55] No differences in graft and patient survival between the two groups were detected at either 1 year or 5 years after transplantation. No additional morbidity or deterioration of preoperative blood pressure and renal function were observed at 1 year in the group with elderly donors. These observations are supported by a study from the Mayo Clinic, which compared the outcomes of 52 recipients of older (>50 years) living donor grafts with a matched group of 103 recipients of younger (<50 years) donor kidneys.[56] Overall graft survival, patient survival and death-censored graft survival, up to 3 years post-transplantation,

did not differ significantly between the two groups.

In contrast to the above findings, significantly poorer survival of grafts from 5 years post-transplantation onwards was detected in a Japanese series of 343 older (>60 years) living donor allografts.[57] Similarly, Prommool *et al.* found donor age to be the most important risk factor for graft loss after the first 5 years.[58] In an analysis of their entire living donor population of 2,540 kidney transplants at the University of Minnesota, Matas and colleagues identified donor age greater than 55 years to be a significant risk factor for late graft loss. This finding was in contrast to a previous study by the same group that showed that increased donor age was not a risk factor for poor outcomes from living donor transplants.[59,60] Nevertheless, long-term survival of grafts from older living donors has been shown to be significantly better than that of organs from elderly deceased donors and similar to that of grafts from younger deceased donors.[60]

The inferior outcomes of an older kidney graft might be a function of the anatomical and physiological changes that occur during aging.[61] Halloran *et al.* have proposed a role for cellular senescence in the decline of renal transplant function over time, pointing out the similarities between some histological features of chronic allograft nephropathy and those of the aging kidney.[62] Functional changes in aging kidneys might be compounded by adverse events in the post-transplantation period (such as warm ischemia, allograft rejection and exposure to nephrotoxic immunosuppression) resulting in a poor graft outcome. The hallmark of renal aging is increased basal renovascular tone accompanied by reduced perfusion, thought to be secondary to glomerulosclerosis.

In individual cases, however, the association between donor age and graft function is weak. Results from the seminal Baltimore Longitudinal Study of Aging have shown that the magnitude of the decline in GFR experienced by healthy elderly subjects was less than was previously estimated. In some elderly subjects, no change in GFR was documented over at least 25 years.[63] So, for a substantial proportion of healthy elderly individuals, GFR remains within the (lower) normal range. GFR is only modestly decreased at the expense of an increased filtration fraction and postglomerular vasoconstriction. Age-related renal function changes are exacerbated by comorbidities such as hypertension, atherosclerosis and heart failure.[64] Not surprisingly, therefore, the medical history of the potential kidney donor yields information useful for prediction of post-transplantation outcomes, independent of donor age. Kidneys from patients dying of cardiovascular events or stroke fail more often than organs from donors dying of subarachnoid hemorrhage.[65] Pre-existing donor hypertension and diabetes negatively influence transplant outcome.[66,67]

Another important factor when considering older living donors is the likelihood of an increased complication rate during procurement of organs. Advances in surgical techniques and anesthesia, and improvements in perioperative care, have made nephrectomy a safe procedure, even for the elderly.[55,60,68] Rates of short-term morbidity and mortality do not seem to be higher for elderly donors, but no data on long-term outcomes for this specific group are available.

It is clear that older potential donors should be accepted only after thorough evaluation and careful screening for conditions that are likely to produce unacceptable operative risk. Healthy donors should not be rejected on the basis of age alone. General health of the donor and functional renal reserve should determine the upper age limit for donation. Donor kidney function, which tends to decline with age, should be balanced against the needs of the recipient. Older living donors and the recipients of their organs should be made aware that allograft function and possibly even graft survival might be compromised by donor age; however, this should not necessarily preclude use of older living donors, as transplantation provides significant advantages over remaining on dialysis while awaiting deceased organ donation.

Elderly recipients

The life expectancy of the general population is increasing consistently, as is the average age of the dialysis population.[3] In most Western countries, the median age of patients on dialysis is approximately 60 years. Advanced recipient age should no longer be a contraindication for renal transplantation, as successful transplantation improves quality of life and survival and reduces costs, even in older recipients.[1,68–70] For patients older than 60 years who are on

transplant waiting lists, the annual death rate is 10%; this rate is 7.4% in transplant recipients. The absolute benefit to patients in this age-group is, therefore, even greater than that observed for 20–39-year-olds, even though more projected life years are gained by transplantation of the latter cohort (17 vs 4 years).[1] Transplant candidates older than 60 years have a fivefold greater likelihood of dying while waiting for a donor kidney than patients under 50 years of age.[3] Prolonged waiting time on dialysis dramatically decreases the clinical and economic benefits of transplantation of older recipients.[71] Early transplantation should, therefore, be strongly encouraged in this group of patients.

In spite of the above data, there is still great reluctance to transplant kidneys in elderly recipients, mainly because of their limited life expectancy. Additionally, in the context of the persistent deceased donor shortage, priority is given to younger patients. Living donor transplantation might, therefore, be particularly beneficial in elderly recipient populations, as it decreases waiting time and enhances patient and allograft survival compared with deceased donor transplantation—effects similar to those observed in younger recipients.[61] Using a living donor negates the argument of organ wasting, and can be a valuable therapeutic option even in the very old. Healthy spouses, siblings and children are potential living donors. (Genetic renal diseases must be ruled out when considering children or siblings as donors.) Furthermore, the selection process for a living donor should include discussion of possibly increased operative and long-term risks in the context of potentially limited benefit to the recipient owing to their short projected life expectancy.

The most common cause of graft loss in elderly recipients is patient death, which is almost four times as likely to occur in recipients older than 65 years than in recipients aged 18–49 years.[70,72] After receipt of an organ from a living donor, survival at 5 years is 93% for younger patients, but only 72% in those older than 60 years. By contrast, death-censored graft survival seems to be better in elderly recipients. In the elderly, the two main causes of post-renal-transplantation morbidity and mortality are cardiovascular disease and infection. Before being accepted onto a transplant waiting list, all older patients should be screened intensively for pre-existing comorbidities. Careful follow-up is mandatory in order to minimize immunosuppression and the occurrence of surgery-related complications.

Elderly recipients seem to have a relatively low risk of acute rejection resulting from age-related deterioration of the immune system. Clinical and experimental studies have shown, however, that recipient age is a strong and independent predictor of the development of chronic allograft failure.[72–74] These findings were reinforced by an analysis restricted to living donor transplants that were not acutely rejected.[72] The pathogenic mechanisms underlying the increased likelihood of chronic allograft failure in elderly patients are not well understood, but probably encompass age-related changes of both immunological and nonimmunological mediators in the recipient, and increased susceptibility to calcineurin inhibitor nephrotoxicity. Tailoring immunosuppressive regimens to account for altered immune responses and increased risks of drug toxicity, infections and cardiovascular disease seems to be the best strategy for improving graft and patient survival in the elderly transplant population.[75]

CONCLUSIONS

Renal transplantation is established as the treatment of choice for ESRD patients in all age-groups. To overcome the organ shortfall, vigorous multipronged strategies to increase the availability of living donors are imperative. These endeavors should include acceptance of genetically unrelated donors (including altruistic donors), development of exchange programs, transplantation across ABO and HLA barriers, and use of expanded-criteria donors, particularly elderly volunteers. It is expected that transplantation of a kidney from an expanded-criteria living donor will be associated with inferior outcomes. It should be emphasized, however, that receiving an allograft from such a donor is preferable to remaining dialysis-dependent on a transplant waiting list. Worldwide, ongoing education of patients and providers, the broadening of regulations to include unrelated living donation, and legislative initiatives removing financial barriers to living donation are required to enhance the potential of this organ source. To minimize the risk to the living donor, ensuring the highest possible standards of clinical care for living donor transplantation has to be our aim. Only then can the enormous benefit of living donor transplantation be maintained for all.

KEY POINTS

- Compared with deceased donor transplantation, transplantation of a kidney from a living donor is associated with superior graft and recipient survival, facilitates pre-emptive transplantation, and expands the total donor pool
- Potential risks to living kidney donors include perioperative morbidity and mortality, renal dysfunction in the long-term, and financial loss
- Strategies to increase the number of living kidney donors include using donors that are genetically unrelated to the recipient, obese, hypertensive or elderly-paired-donor kidney exchanges, and transplantation across ABO and HLA barriers
- Successful promotion of living kidney donation requires legislative reform, education of patients and providers, and commitment to high-quality, long-term follow-up of living donors

References

1 Wolfe RA *et al*. (1999) Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* **341:** 1725–1730
2 Satayathum S *et al*. (2005) Kidney transplantation and wait-listing rates from the international Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* **68:** 330–337
3 Cohen B *et al*. (2005) Expanding the donor pool to increase renal transplantation. *Nephrol Dial Transplant* **20:** 34–41
4 Cosio FG *et al*. (1998) Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. *Kidney Int* **53:** 767–772
5 Meier-Kriesche HU and Kaplan B (2002) Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation* **74:** 1377–1381
6 Meier-Kriesche HU *et al*. (2000) Effect of waiting time on renal transplant outcome. *Kidney Int* **58:** 1311–1317
7 Sheehy E *et al*. (2003) Estimating the number of potential organ donors in the United States. *N Engl J Med* **349:** 667–674
8 Hariharan S *et al*. (2000) Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* **342:** 605–612
9 Papalois VE *et al*. (2000) Pre-emptive transplants for patients with renal failure: an argument against waiting until dialysis. *Transplantation* **70:** 625–631
10 Mange KC *et al*. (2001) Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors. *N Engl J Med* **344:** 726–731
11 Kasiske BL *et al*. (2002) Preemptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol* **13:** 1358–1364
12 Roodnat JI *et al*. (2003) The superior results of living-donor renal transplantation are not completely caused by selection or short cold ischemia time: a single-center, multivariate analysis. *Transplantation* **75:** 2014–2018
13 Terasaki PI *et al*. (1995) High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med* **333:** 333–336
14 Gjertson DW and Cecka JM (2000) Living unrelated donor kidney transplantation. *Kidney Int* **58:** 491–499
15 Matas AJ *et al*. (2003) Morbidity and mortality after living kidney donation, 1999–2001: survey of United States transplant centers. *Am J Transplant* **3:** 830–834
16 Fehrman-Ekholm I *et al*. (1997) Kidney donors live longer. *Transplantation* **64:** 976–978
17 Narkun-Burgess DM *et al*. (1993) Forty-five year follow-up after uninephrectomy. *Kidney Int* **43:** 1110–1115
18 Ramcharan T and Matas AJ (2002) Long-term (20–37 years) follow-up of living kidney donors. *Am J Transplant* **2:** 959–964
19 Ellison MD *et al*. (2002) Living kidney donors in need of kidney transplants: a report from the organ procurement and transplantation network. *Transplantation* **74:** 1349–1351
20 Delmonico F (2005) A report of the Amsterdam Forum On the Care of the Live Kidney Donor: data and medical guidelines. *Transplantation* **79 (Suppl 2):** S53–S66
21 Magee CC and Pascual M (2004) Update in renal transplantation. *Arch Intern Med* **164:** 1373–1388
22 Gjertson DW (2003) Look-up survival tables for living-donor renal transplants: OPTN/UNOS data 1995–2002. In *Clin Transpl*, 337–386 (Eds Cecka JM and Terasaki PI) Los Angeles: UCLA Immunogenetics Center
23 Cecka JM (2003) The OPTN/UNOS Renal Transplant Registry 2003. In *Clin Transpl*, 1–12 (Eds Cecka JM and Terasaki PI) Los Angeles: UCLA Immunogenetics Center
24 Adams PL *et al*. (2002) The nondirected live-kidney donor: ethical considerations and practice guidelines: A National Conference Report. *Transplantation* **74:** 582–589
25 Jacobs CL *et al*. (2003) Evolution of a nondirected kidney donor program: lessons learned. In *Clin Transpl*, 283–291 (Eds Cecka JM and Terasaki PI) Los Angeles: UCLA Immunogenetics Center
26 Park K *et al*. (1999) Exchange-donor program in kidney transplantation. *Transplant Proc* **31:** 356–357
27 Park K *et al*. (1999) Exchange donor program in kidney transplantation. *Transplantation* **67:** 336–338
28 Park K *et al*. (2004) Exchange living-donor kidney transplantation: diminution of donor organ shortage. *Transplant Proc* **36:** 2949–2951
29 Davis CL and Delmonico FL (2005) Living-donor kidney transplantation: a review of the current practices for the live donor. *J Am Soc Nephrol* **16:** 2098–2110
30 Segev DL *et al*. (2005) Kidney paired donation and optimizing the use of live donor organs. *JAMA* **293:** 1883–1890
31 Kaplan I *et al.* (2005) A computer match program for paired and unconventional kidney exchanges. *Am J Transplant* **5:** 2306–2308
32 Saidman SL *et al*. (2006) Increasing the opportunity of live kidney donation by matching for two- and three-way exchanges. *Transplantation* **81:** 773–782
33 Montgomery RA *et al*. (2006) Domino paired kidney donation: a strategy to make best use of live non-directed donation. *Lancet* **368:** 419–421
34 Roth AE *et al*. (2006) Utilizing list exchange and nondirected donation through 'chain' paired kidney donations. *Am J Transplant* **6:** 2694–2705
35 Baid S *et al*. (2001) Managing the highly sensitized transplant recipient and B cell tolerance. *Curr Opin Immunol* **13:** 577–581
36 Stegall MD *et al*. (2004) ABO-incompatible kidney transplantation. *Transplantation* **78:** 635–640
37 Montgomery RA and Zachary AA (2004) Transplanting patients with a positive donor-specific crossmatch: a single center's perspective. *Pediatr Transplant* **8:** 535–542

38 Montgomery RA *et al*. (2000) Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation* **70:** 887–895
39 Glotz D *et al*. (2002) Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). *Am J Transplant* **2:** 758–760
40 Jordan SC *et al*. (2003) Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. *Transplantation* **76:** 631–636
41 Gloor JM *et al*. (2003) Overcoming a positive crossmatch in living-donor kidney transplantation. *Am J Transplant* **3:** 1017–1023
42 Warren DS *et al*. (2004) Successful renal transplantation across simultaneous ABO incompatible and positive crossmatch barriers. *Am J Transplant* **4:** 561–568
43 Takahashi K *et al*. (2004) Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. *Am J Transplant* **4:** 1089–1096
44 Tyden G *et al*. (2005) The Stockholm experience with ABO-incompatible kidney transplantations without splenectomy. *Xenotransplantation* **13:** 105–107
45 Sonnenday CJ *et al*. (2004) Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. *Am J Transplant* **4:** 1315–1322
46 Haas M *et al*. (2006) C4d and C3d staining in biopsies of ABO- and HLA-incompatible renal allografts: correlation with histologic findings. *Am J Transplant* **6:** 1829–1840
47 Textor SC *et al*. (2004) Blood pressure and renal function after kidney donation from hypertensive living donors. *Transplantation* **78:** 276–282
48 Pesavento TE *et al*. (1999) Obese living kidney donors: short-term results and possible implications. *Transplantation* **68:** 1491–1496
49 Praga M *et al*. (2000) Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. *Kidney Int* **58:** 2111–2118
50 Basar H *et al*. (1999) Renal transplantation in recipients over the age of 60: the impact of donor age. *Transplantation* **67:** 1191–1193
51 Smits JM *et al*. (2000) Permanent detrimental effect of nonimmunological factors on long-term renal graft survival: a parsimonious model of time-dependency. *Transplantation* **70:** 317–323
52 Kasiske BL and Snyder J (2002) Matching older kidneys with older patients does not improve allograft survival. *J Am Soc Nephrol* **13:** 1067–1072
53 Woo YM *et al*. (2005) The advanced age deceased kidney donor: current outcomes and future opportunities. *Kidney Int* **67:** 2407–2414
54 Meier-Kriesche HU *et al*. (2002) Interaction between donor and recipient age in determining the risk of chronic renal allograft failure. *J Am Geriatr Soc* **50:** 14–17
55 Kumar A *et al*. (2000) Long-term followup of elderly donors in a live related renal transplant program. *J Urol* **163:** 1654–1658
56 Pena De La Vega LS *et al*. (2004) Patient and graft outcomes from older living kidney donors are similar to those from younger donors despite lower GFR. *Kidney Int* **66:** 1654–1661
57 Toma H *et al*. (2001) Time-dependent risk factors influencing the long-term outcome in living renal allografts: donor age is a crucial risk factor for long-term graft survival more than 5 years after transplantation. *Transplantation* **72:** 940–947
58 Prommool S *et al*. (2000) Time dependency of factors affecting renal allograft survival. *J Am Soc Nephrol* **11:** 565–573
59 Matas AJ *et al*. (2001) 2,500 living donor kidney transplants: a single-center experience. *Ann Surg* **234:** 149–164
60 Kerr SR *et al*. (1999) Living donors > 55 years: to use or not to use? *Transplantation* **67:** 999–1004
61 Baid-Agrawal S *et al*. (2004) WCN 2003 satellite symposium on kidney transplantation in the elderly, Weimar, Germany, June 12–14, 2003. *Nephrol Dial Transplant* **19:** 43–46
62 Halloran PF *et al*. (1999) Rethinking chronic allograft nephropathy: the concept of accelerated senescence. *J Am Soc Nephrol* **10:** 167–181
63 Lindeman RD *et al*. (1985) Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* **33:** 278–285
64 Fliser D (2005) Ren sanus in corpore sano: the myth of the inexorable decline of renal function with senescence. *Nephrol Dial Transplant* **20:** 482–485
65 Troppmann C *et al*. (1991) Donor age and cause of death affect cadaver renal allograft outcome. *Transplant Proc* **23:** 1365–1366
66 Carter JT *et al*. (2000) Evaluation of the older cadaveric kidney donor: the impact of donor hypertension and creatinine clearance on graft performance and survival. *Transplantation* **70:** 765–771
67 Ojo AO *et al*. (2000) Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. *Am J Kidney Dis* **36:** 153–159
68 Fritsche L *et al*. (2003) Old-for-old kidney allocation allows successful expansion of the donor and recipient pool. *Am J Transplant* **3:** 1434–1439
69 Noeldeke J *et al*. (2006) Prospective age-matching in elderly kidney transplant recipients—a 5-year analysis of the eurotransplant senior program [abstract # 223]. *Am J Transplant* **6 (Suppl 2):** a141
70 Oniscu GC *et al*. (2004) How old is old for transplantation? *Am J Transplant* **12:** 2067–2074
71 Jassal SV *et al*. (2003) Kidney transplantation in the elderly: a decision analysis. *J Am Soc Nephrol* **14:** 187–196
72 Meier-Kriesche HU *et al*. (2000) Relationship of recipient age and development of chronic allograft failure. *Transplantation* **70:** 306–310
73 Martins PN *et al*. (2005) Age and immune response in organ transplantation. *Transplantation* **79:** 127–132
74 Pascher A *et al*. (2004) Modifications of immune regulations with increasing donor & recipient age. *Ann Transplant* **9:** 72–73
75 Morales JM *et al*. (2000) Immunosuppression in older renal transplant patients. *Drugs Aging* **16:** 279–287

Competing interests
The authors declared they have no competing interests.