Expanding criteria for living kidney donors: what are the limits?

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Abstract

The need to evaluate potential living kidney donors is more pressing than ever before. Evaluating the potential medical risks to individual donors presents both medical and ethical questions related to quantitative hazards of donor nephrectomy. These include conditions commonly associated with age, such as the decline in glomerular filtration rate, the rise in arterial pressures, and weight gain. The “normal” ranges for many of these characteristics are changing as their importance as predictors of cardiovascular risk is reevaluated and the duration of exposure for a lifetime is considered. Many older donors in good health favor donating a kidney to a spouse, despite the presence of elevated blood pressure or even impaired glucose tolerance. The Mayo Kidney/Pancreas transplant program established an “extended criteria workgroup” to address these issues on an individual basis. Our program now stratifies medical criteria based upon age, allowing more liberal criteria for older donors. As a result, we accept treated hypertension in white donors, emphasizing the importance of informed consent and the need for vigilant follow-up. Our greatest concern relates to the development of obesity, particularly in younger individuals. Many of the long-term results of kidney donation are likely to hinge upon future behavior, including smoking, weight management, and medical follow-up care. Older donors are more likely to have established behavior patterns, an element that makes them better candidates in many respects. Studies to closely track the impact of donor nephrectomy in the current era with changing population demographics and expectations are essential.© 2008 Elsevier Inc. All rights reserved.

1. Introduction

The waiting list for kidney transplantation continues to grow and now exceeds the yearly number of transplants by several-fold. Waiting times for deceased donors now exceed 4 years in many regions of the United States. One result of this trend is a continued demand for living kidney donors and renewed consideration of the criteria by which such donors are selected.

Living kidney donors also provide substantial clinical benefits, including improved early and long-term graft function. Improvements in donor surgery using laparoscopic donor nephrectomy and more potent recipient immunosuppression that minimizes the advantages of genetic haplotype matching have combined to expand acceptance of living genetically unrelated kidney donors. In 2001, the number of living donors exceeded the number of deceased donors for the first time. Some centers now consider “nondirected” kidney donation settings in which the donor and recipient have no relationship beforehand whatsoever [1].

These developments have expanded the need to evaluate potential living kidney donors in many transplant programs. The Mayo Clinic Kidney/Pancreas program now evaluates more than 300 kidney donor candidates annually. In response, our group has chosen to examine and to define carefully the medical parameters by which this process occurs. Both the processes and outcomes for potential donors face closer public scrutiny than ever before. Some authors in the popular press have raised public concern, suggesting that organ donors are “exploited” and may not be informed of the risks they are assuming. This issue is particularly pointed considering the expansion of Internet connections by which donors and recipients are now meeting [2].

The element of “informed consent” is central to the discussion of ethical validity of pursuing living kidney donation. What exactly are the risks being assumed by the potential donor as a result of donor nephrectomy? Because we encounter more individuals coming forward as donor candidates, clinicians now must more openly and precisely define these terms. Published acceptance criteria were often derived empirically on a “temporary basis” 50 years ago when the first donor-recipient pairs were identified.
This discussion will focus on the topic of defining and expanding medical criteria for potential living kidney donors. Recent surveys emphasize the variability between transplant programs and changing criteria for the past decade [3]. We will focus upon the process within the Mayo Clinic Kidney/Pancreas transplant program because it has developed for the past decade, particularly in regard to considerations of age, blood pressure, and obesity, including the prospects for future development of diabetes and the metabolic syndrome. Our program established a committee (designated “extended criteria donor workgroup”) with responsibility for reviewing and defining both medical and psychosocial criteria to provide guidelines to be applied by individual clinicians throughout the transplant program.

2. The issue of age

Many centers impose age limitations, usually requiring that potential donors be older than 18 years (required for legal consent) and younger than some upper age limit. The mean age for published series of donors was previously near 30 years with those older than 50 years considered “older donors” [4]. This focus upon younger donors, in part, reflects selection in favor of optimizing the outcome for the recipient, considering that such individuals have excellent kidney function. Published outcomes with deceased donors commonly cite age and death from stroke or other cardiovascular disease as having a negative impact on recipient and graft survival. It has been assumed that similar arguments might apply to living donors.

Demographics of both potential recipients and donors are changing, however. Individuals older than 65 years now represent the fastest growing segment of patients with end-stage renal disease (ESRD). Many of these now consider transplantation as an optimal renal function replacement and may have a spouse, sibling, or friend of similar age available as a potential donor. In our own program, 26.3% of 584 potential donors in recent years were older than 50 years. The absolute levels of kidney function are slightly lower in this age group, as compared with donors at younger ages. Follow-up studies for patients receiving kidneys from older living donors indicate that immediate levels of glomerular filtration rate are slightly lower, but that they are satisfactory for excellent patient and graft survival [5]. Kidney function remains stable for the initial several years of follow-up comparable with recipients from younger donors.

This trend appears to be common throughout the United States. Recent surveys indicate that many more programs now extend upper age limits and many have “no upper limit” [3]. It may be argued that matching donor and recipients ages has an added value of matching “net benefit” more closely than otherwise possible. Some authors argue that mismatch of donor ages (as applied in deceased donor allocation based simply on waiting times) allows some older recipients to receive younger kidneys and effectively “waste” some of the potential long-term benefit if they die with a functioning graft [6]. Such age mismatches have the adverse effect of occasionally providing younger recipients with much older kidneys, leading to the need for retransplantation. Expanding the age range of potential donors does introduce the issues of changes associated with aging, including development of systemic hypertension.

3. Hypertension

Blood pressure rises in Western societies as a function of age [7]. This phenomenon is present in potential living kidney donors as illustrated in Fig. 1. Arterial hypertension is among the strongest predictors of cardiovascular risk, particularly stroke and coronary artery disease. In subjects with malignant hypertension in the past, progressive renal insufficiency was often observed and formed the basis for considering hypertension as excluding a potential living kidney donor.

Whether lesser degrees of hypertension without manifest target organ damage pose a risk to renal function is far less clear. Epidemiologic studies including screenees for the Multiple Risk Factor Intervention Trial indicate that arterial pressure during a single screening visit does provide a general prediction of those most likely to develop advanced kidney failure 16 years later [8]. This effect is modest for whites but associated with 4- to 6-fold higher absolute and attributable risk for African American subjects. Subsequent studies from the same data set indicate that most of this risk developed in individuals with identified diabetes at the time.
of screening [9]. The absolute risk of ESRD in those without diabetes was extremely low. Follow-up studies of more than 25,000 patients included in the initial hypertension treatment trials identified both low rates of developing kidney disease and no difference between treated and placebo groups [10]. Such observations lead some authors to question whether moderate blood pressure elevations in fact produce kidney injury at all [11].

Recent population-based epidemiologic data again provide some insight in this regard. Long-term follow-up of individuals screened at the Kaiser-Permanente programs indicates that a small gradient of progressive risk can indeed be predicted by initial clinic blood pressure readings. The time-dependent magnitude of this risk is illustrated in Fig. 2 [12]. These data argue that a small risk (<1.0%) of renal failure accrues for the highest blood pressure groups during follow-up periods exceeding 30 or 40 years of exposure. A generally similar observation is available from long-term studies of Japanese subjects, in which arterial pressure generally predicts the level of proteinuria, which is a strong predictor of the long-term risks of ESRD. The absolute risk in this population was 0.5% for a follow-up of 17 years.

Remarkably, the level of blood pressure defined as “hypertension” has changed substantially during the period of living donor kidney transplantation. At the time of reporting outcomes in the 1980s, the threshold level for defining hypertension was an office reading above 160/95 mm Hg [13]. Since then, the Joint National Committee reports defining treatment recommendations for hypertension have reset the threshold for definite hypertension at 140/90 mm Hg and consider less than 120/80 mm Hg to be “normal.” The range between 120 and 139/81-89 mm Hg is now designated “prehypertension” [14]. The definition of risk in this set of recommendations is almost entirely related to established benefits regarding reduction of stroke and other vascular events. More aggressive goals of therapy to below 130/80 mm Hg are recommended for individuals considered at high cardiovascular risk, particularly those with diabetes and/or proteinuric kidney disease.

Because blood pressures rise with age, the fraction of individuals identified as “hypertensive” in the US population rises with age also. Blood pressure measurements in the clinic and using an oscillometric recorder during later hemodynamic measurements for 584 potential living kidney donors are illustrated in Fig. 1. The variability in arterial pressures is well recognized, making it difficult to classify individuals on the basis of a few readings. For that reason, our program and others have advocated systematic inclusion of ambulatory blood pressure monitoring to more precisely define blood pressure status [15].

But do the blood pressure levels now defined as hypertensive pose a long-term hazard to individuals that donate a kidney? We argue that, for most individuals, effective blood pressure therapy is warranted for hypertension regardless of whether they donate a kidney or not. It may be argued that the definable benefits regarding antihypertensive therapy appear to relate most closely to the level of blood pressure achieved rather than the use of any particular drug or other therapeutic maneuver [16]. Even for individuals with proteinuric kidney disease associated with diabetes, the rates of progression are closely linked to achieved arterial pressure. As an isolated medical abnormality, modest high blood pressure appears to confer little specific risk to kidney function in white subjects, if it is adequately treated. For those reasons, we have implemented a policy of accepting potential white donors older than 40 years with moderate blood pressure elevation if it can be treated with a reasonably simple regimen and no other major medical issues are present.

Follow-up studies to this point are limited. We have contacted the early donors (now 5 years after donation) and have been reassured that no major abnormalities have arisen. Donor follow-up reports from subjects accepted during the 1970s and 1980s have been reassuring despite the fact that higher arterial pressures were accepted during those periods. Donor follow-up has proven to be difficult for all programs, however. Reports of donors now reaching advanced kidney dysfunction and becoming candidates for kidney transplantation themselves are not common but do occur. In some cases, no cause is evident and kidney dysfunction is attributed to “hypertensive nephrosclerosis” [17]. This report emphasizes that age at donation was 31 years and the mean time to develop ESRD was more than 15 years after organ donation.

4. Stratification by age

One of the major developments in our own program for donor selection is the use of risk stratification as a function of
age. If some factors, such as elevated arterial pressures, pose a long-term potential hazard, perhaps they should be ranked differently depending upon the likely duration of exposure to this risk. What may be considered an acceptable risk for a 55-year-old donor may be an unacceptable risk in a 25-year-old donor. This approach includes both an estimate of the risk itself and recognition that many of these concerns depend directly upon “future behavior.” In the case of hypertension, for example, the likelihood of an individual continuing medical follow-up, having sustained medical insurance coverage, and having the maturity to modify risk favorably is more likely in an older individual than a younger one. Many subjects in their twenties do not have reliable employment, insurance coverage, or follow-up arrangements. The role of behavior regarding additional risk, such as smoking, weight gain, and medication adherence, is less fixed during these years. As a result, we set specific threshold arterial pressures and treatment requirements differently for those older and younger than 40 years.

5. Body weight, glucose tolerance, and the metabolic syndrome

Among the most worrisome features of donor demographics in the United States is the rise in prevalent obesity, much of which has occurred after 1980 [18]. In our own program, fully 29.8% of potential donors have a body mass index (BMI) above 30 kg/m². The rise in obesity has been paralleled by rising prevalence of both glucose intolerance (or “prediabetes”) and combined lipid abnormalities designated “the metabolic syndrome” [19]. It is inescapable that some individuals now presenting as donors will develop overt diabetes and be at risk for both cardiovascular and renal complications in future years. Whether they will be at increased risk for morbidity and mortality by virtue of having donated a kidney is not clear but cannot be reasonably excluded.

Excluding donors with demonstrable diabetes is universally accepted among transplant centers [20]. How best to evaluate and consider the future risk of developing diabetes is not well defined and varies considerably between programs surveyed as recently as 2005 [3].

Recent studies emphasize the independent role of obesity itself as an accelerant to some forms of glomerular disease [21]. Long-term follow-up of subjects undergoing nephrectomy for other reasons indicates that the prevalence of proteinuria and some degree of renal insufficiency (rise in serum creatinine) is related most directly to the presence of a BMI above 30 kg/m² [22]. Other studies indicate no major hazard related to obesity as regards measured kidney function alone [23], although it is recognized that BMI does predict some elements of future morbidity and mortality. Epidemiologic associations from the Kaiser-Permanente data set again pose time-dependent risks predicted by obesity that are, in fact, considerably greater in magnitude than those associated with arterial pressure. These estimates are illustrated in Fig. 3 [24]. Whether these risks are magnified by having a single kidney is not known, but it has been suggested on the basis of “hyperfiltration” mechanisms. Morphometric analyses of implantation biopsies from obese donors confirm that such kidneys have larger glomerular volumes and appear to have changes associated with hyperfiltration [25]. In our program, selection criteria include establishing normal levels of urinary microalbumin excretion. This provides additional reassurance of limited cardiovascular risk associated with microalbuminuria.

6. The role of behavior

One might argue that weight gain is but one aspect of concerns related to “future behavior.” Established obesity is at least in part a function of lifestyle and choices reflecting an individual’s behavior over time. Treatment options have heretofore proven to be of limited efficacy, in contrast to antihypertensive therapy. This may be another instance where age provides a longer-term view applicable to the suitability of a potential kidney donor. It may be argued that habits of body weight, exercise, alcohol use, and self-care are more clearly established in older age brackets, for example, older than 50 years, than they are at younger age brackets, for example, between 20 and 30 years. As a result, our own program stratifies acceptable levels of blood pressure, blood glucose, and glomerular filtration rate by age for potential donors, and we are considering making the same distinctions for body weight.

The issue of donor outcomes is more pressing than ever before. More individuals are coming forward to be
considered as potential kidney donors, with the assumption that prior experience has established the safety of this procedure. The Mayo Clinic Kidney/Pancreas transplant program accepts the notion that expanding medical criteria for living kidney donors carries an obligation to study and define their outcomes. Some of our studies are directed to that aim already but will require many years to complete. A multicenter study funded through the National Institutes of Health entitled Renal and Lung Living Donors Evaluation Study (RELIVE) seeks to define more precisely the mortality, characteristics, and renal functional outcomes for previous living donors for kidney and lung transplants. This study will focus on previous donors and may not reflect the demographic trends of more recent years.

The ethical concerns facing transplantation in this regard are complex. One must accept that any surgical procedure carries risk. Hence, it is not the issue of whether kidney donation is safe but of quantifying how much risk is incurred by living kidney donors and over what period. We believe that these should be recognized as dynamic questions, considering both the individual characteristics of the donor at the time of evaluation, age-related duration of risk and future risk exposure, as well as estimates of future behavior. How best to quantify and follow these risks present major challenges to solid organ transplantation. This is an area in which vast benefits are possible to patients experiencing kidney failure and for which altruistic individuals have an opportunity to provide a major service. Fairly evaluating and presenting potential organ donors with a realistic understanding of the hazards they are accepting will become an increasingly vital part of clinical transplantation.

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References