

The Living Kidney Donor Evaluation: Focus on Renal Issues

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Summary

Living kidney donor evaluations and follow-up have previously been addressed mostly by transplant physicians and surgeons. However, this area is significantly informed by basic principles of renal physiology and is of increasing clinical interest to general nephrologists. The general nephrology community is increasingly involved in evaluating the suitability of potential donors and in following them after donation when questions are raised about low GFR, hypertension, and other renal concerns. This article focuses on some of the most central and common issues that arise in evaluating potential donors and attempts to provide guidance on the basis of our review of the living donor literature, extrapolations from the general nephrology literature, and our own clinical experience.

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Introduction

The first successful kidney transplant was performed between identical twins in 1954. Since then, there has been a substantial increase in living kidney transplants. Currently, more than 6000 are performed each year in the United States alone. One factor underlying this increase in living donor transplantation is the belief that donors have minimal perioperative and long-term risks from nephrectomy. A perioperative mortality of 3 in 10,000 was assessed by a survey of transplant centers in 1992 (1) and confirmed recently from Organ Procurement and Transplantation Network (OPTN) data combined with the Social Security Death Master File (2). Perioperative morbidity from an older single-center study shows rates of 0.2% and 8% for major and minor complications, respectively (3), whereas newer data from Norway and US data registries using standardized grading show rates of 3%–4% and 10%–18% for major and minor complications, respectively (4,5).

Minimal long-term risks of nephrectomy were initially shown in World War II servicemen who underwent uninephrectomy compared with non-nephrectomized servicemen (6), and also in donors compared with nondonating siblings (1). More recent studies have also shown excellent long-term outcomes in donors compared with age-matched general populations (7,8). However, these studies were limited to young, Caucasian donors, and current donors are increasingly older, obese and hypertensive (9). Medically complex donors form a significant proportion (24%, defined as presence of hypertension, obesity, or an eGFR <60) (10) of current donors and an even bigger fraction of those that are evaluated. There are few data on the long-term effects of donation in this population, and the few available studies are small, with heterogeneous definitions (11,12). Currently, most US transplant centers do not have long-term

donor follow-up beyond the immediate postoperative period (13). Whether more medically complex donors have similar outcomes remains unanswered. Lack of long-term data makes it difficult to make evidence-based recommendations about potentially higher-risk subgroups. In such a setting, clinicians make individualized decisions and this leads to significant variability in the selection practices of centers across the United States (10,14).

Because of the nature of living donation, there can be no randomized controlled trials of living donors to determine either the appropriate testing required to evaluate donors or the absolute criteria for accepting a donor. However, some general guidelines have been published, including the results of the International Forum for the Care of the Live Kidney Donor held in Amsterdam in 2004 (15). The usual workup for donor evaluation is summarized in Table 1. Absolute and relative contraindications are summarized in Table 2. Some of the key renal issues pertaining to the selection and risks for donors are discussed below. It is important to remember that for all of the issues discussed below, the cut-offs should not be rigidly applied. The potential donor should be evaluated as a whole, and risk due to a specific medical finding should be assessed in the context of other potential risk factors. For example, a 25-year-old African-American man with a body mass index (BMI) of 30 and borderline BP has substantial lifetime risk of developing ESRD and would usually be excluded from donation, even if none of his risk factors are individually an absolute contraindication. In contrast, a 65-year-old Caucasian with well controlled hypertension (no end organ damage) but who has no other risk factors is likely at low lifetime risk of developing ESRD and hence could be considered for donation.

The emotional relationship between donor and recipient may also be important. Given the high mortality

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of prolonged dialysis, some donors may wish to accept higher risks than might typically be recommended. For example, someone wishing to donate to a spouse might accept higher than usual risk from donation to derive direct benefits from having a healthy spouse. In such a situation, it may be reasonable to proceed with donation, after thorough discussion of the risks and informed consent. However, it is important to remember that the primary responsibility of the donor physician is to “first, do no harm,” and hence to sometimes restrain motivated donors from harming themselves.

Table 1. Evaluation of donors

<p>Blood group, HLA typing and cross-match Assessment of BP and body mass index Complete physical examination Complete blood count and coagulation profile Electrolytes and liver function tests Fasting glucose and lipid profile HbA1c or glucose tolerance test if high risk for diabetes Pregnancy test (if indicated) Infection screen hepatitis B and C syphilis HIV cytomegalovirus and Epstein–Barr virus screening for tuberculosis if indicated: toxoplasma, strongyloides, trypanosoma, West Nile, malaria and others Estimation of GFR by 24-h creatinine clearance or measurement of GFR using iodinated or radioactive isotopes Urinalysis Urine culture if indicated Assessment of proteinuria: 24-h protein excretion or spot protein/creatinine ratio Chest radiograph Electrocardiogram Stress test and echocardiography as needed Assessment of renal anatomy: Spiral computed tomography or magnetic resonance angiography Cancer screening: prostate-specific antigen, colonoscopy, mammography, Pap smear as recommended for the general population</p>
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Age

Although older donors are more likely to have complex medical histories and lower GFRs, studies have shown similar outcomes in selected older donors versus younger donors for perioperative outcomes such as operative time, blood loss, and length of stay (16–18). With regard to long-term risks, older donors with potential risk factors for kidney disease, such as hypertension, are less likely than younger donors to have enough time for such risk factors to lead to kidney disease or for any kidney disease that develops to affect life expectancy (19). As a result, most US transplant programs currently do not have an upper age limit for accepting donors and are more flexible in applying exclusion criteria for renal risk factors in older donors (14). With respect to lower age limits, most programs do not consider donors aged <18 years and consider age of 18–21 years as a relative contraindication. Younger donors, even if without risk factors for kidney disease at the time of evaluation, may still develop diabetes, hypertension, obesity, or other renal risk factors, and have more time for these risk factors to progress to CKD and ultimately ESRD. Support for this notion is provided by OPTN data, which show that most of the donors that were placed on the transplant waiting list had donated between the ages of 18 and 34 years and developed ESRD >15 years after donation (20). Younger potential donors with presence of even borderline risk factors are likely at higher long-term risk and we would recommend using the exclusion criteria more stringently in this population.

GFR

A direct measure of GFR using iodinated or radioactive isotopes is ideal for evaluating kidney function in donors. However, most US centers do not have these measures available and use 24-hour urine collections to calculate creatinine clearance (14). These urine collections are subject to patient error, but the adequacy of collections can usually be confirmed if they contain 20–25 mg creatinine/kg body weight for men and 15–20 mg/kg for women (21,22). eGFR based on the Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration, and other equations based on serum creatinine has been compared with measured GFR, although not with creatinine

Table 2. Absolute and relative contraindications

Absolute Contraindications	Relative Contraindications
Age <18 yr	Age 18–21 yr
Mentally incapable of making informed decision	Creatinine clearance <2 SD below mean for age
Uncontrolled hypertension or hypertension with end organ damage	Hypertension in non-Caucasian race
Diabetes	Hypertension in young donor
BMI >35	Prediabetes in young donor
Active malignancy or incompletely treated malignancy	BMI >30
Untreated psychiatric conditions	Microalbuminuria or proteinuria
Nephrolithiasis with high likelihood of recurrence	Bleeding disorder
Evidence of donor coercion	History of thrombosis or embolism
Persistent infection	Nephrolithiasis
	History of malignancy, especially if metastatic
	Significant cardiovascular disease

clearance, and is unreliable for evaluation of donors and thus should be avoided (23,24). Although many programs have reported using a lower limit for creatinine clearance of 80 ml/min per 1.73 m² (14), the use of a single cut-off value does not take into account the well known decline in the GFR with aging (23,25–27). Therefore, to identify potential donors at increased risk of developing ESRD, cut-offs should vary based on age. Unfortunately, there are relatively few published data on kidney function in normal populations stratified by age. The best available creatinine clearance data comes from the Baltimore study in 1976, and is summarized in Table 3 (27). Creatinine clearance is usually 10%–20% higher than the GFR, and several tables of GFRs stratified by age have been published. For example, the Kidney Disease Outcomes Quality Initiative guidelines (28) reproduce data from the Baltimore study in 1950, which used inulin clearance to measure the GFR (25). However, these measures were on hospitalized patients and included 12 or fewer participants in each age group, and thus are not a good representation of the general population. More recent studies (23,29) reported iothalamate GFRs in a large number of participants who donated kidneys. These data do not represent true cross-sections of the population, but may help guide programs using measured GFRs in potential donors.

Although various reports of normal kidney function stratified by age differ somewhat, due to the technique used and the proportion of patients with medical problems that are included, the importance of using different cut-offs depending on the age of the potential donor can be seen from any of the reports. For example, Table 3 shows that a creatinine clearance of 80 ml/min per 1.73 m² would be of relatively little concern for a 66-year-old donor, because that value is within 2 SDs of the mean for that age and there are relatively few years at risk during which that donor might develop ESRD. In contrast, the same GFR of 80 ml/min per 1.73 m² in a 30-year-old donor is much lower than 2 SDs below the mean for that age, and the 30-year-old donor has substantially more years at risk during which he or she will have declining kidney function and might develop ESRD. By definition, excluding donors with creatinine clearance or a GFR below the mean for age – 2 SD would exclude the 2.2% of the population with the lowest kidney function. Of note, males have a higher mean GFR for age than females, but these sex differences disappear after correction for body surface area (23).

No prospective study has determined what threshold should be used for selecting donors for either measured GFR, creatinine clearance, or creatinine-based equations. A frequently cited study by Nordén *et al.* (30) showed that transplants from living donors with a GFR <80 ml/min (not adjusted for body surface area) had graft survival worse than living transplants with higher GFR and similar to cadaveric transplants. This highlights the fact that the evaluation of kidney function is important not only to protect the health of a donor, but also to ensure adequate function for the recipient. Based on the study by Nordén *et al.* (30), 80 ml/min is a rough guide as to the minimum donor GFR required for most recipients. However, there are cases in which accepting a lower GFR might be acceptable for both donor and recipient. For example, a 70-year-old donor with a creatinine clearance of 78 ml/min per 1.73 m² has renal function that is within 2 SDs of the mean for his age, and would likely provide adequate renal function for a 70-year-old recipient.

Racial Variation

It is well recognized that African Americans have a higher incidence of ESRD than Caucasians (31,32). Similarly, the incidence of renal failure is higher in African Americans after donation compared with other races. Analysis of OPTN data reveals that African Americans comprised only 14% of living kidney donors but were 43% of former donors who were listed for transplant (20). Higher incidence of hypertension, diabetes, CKD, and cardiovascular disease has been noted in African-American former donors compared with Caucasians; however, this higher incidence is similar to that of African Americans in the general population (National Health and Nutrition Examination Survey data) (33). When African-American donors were compared with their race-matched NHANES controls in terms of post-donation mortality, the African-American donors had a lower mortality, similar to lower mortality seen in other donors compared with controls (2). Recent evidence suggests that the higher incidence of FSGS and hypertension-related ESRD in African Americans is associated with specific polymorphisms in gene APOL1 (34). Approximately 10% of African Americans possess two risk alleles, whereas 49% lack risk alleles. A recent study suggests that deceased donor kidneys with two risk alleles are associated with earlier and higher rates

Table 3. Measured creatinine clearance according to age

Age (yr)	Mean Creatinine Clearance (ml/min per 1.73 m ²)	SD	Mean – SD	Mean – 2 SD
17–24	140	12	128	116
25–34	140	21	119	98
35–44	133	20	113	93
45–54	127	17	110	93
55–64	120	16	104	88
65–74	110	16	94	78
75–84	97	16	81	65

Modified from Rowe *et al.* (27).

of graft loss in recipients (35). Although there are currently no data on the effect of risk allele testing on future outcomes in donors, if the predictive value of APO11 is confirmed in future studies, then it may allow for exclusion of African Americans with these two risk alleles and allow others to be safely accepted.

Hypertension

Donors should be screened for hypertension with two or more properly measured, seated BP readings on two or more visits (36). If BP is high and there is concern for white-coat hypertension, then ambulatory BP monitoring should be considered (36). The risks of donation in mild, well controlled hypertension are not well documented. This leads to substantial variability in inclusion and exclusion of such donors. Although 47% of US programs will exclude potential donors taking any antihypertensive medications, 41% of programs will accept patients with well controlled hypertension taking a single agent and exclude donors taking more than one medication (14). Good short-term outcomes have been shown in selected Caucasian donors with mild hypertension (37). In considering a donor with hypertension, we suggest that evidence for end organ damage (left ventricular hypertrophy and retinopathy) should be sought and used to exclude the candidate. We agree with the Amsterdam forum recommendations that candidates with BP >140/90 are not acceptable as donors but some with easily controlled BP with certain other defined criteria (*e.g.*, age >50 years, GFR >80 ml/min, urine albumin <30 mg/d) may be considered low risk for developing kidney disease and hence acceptable as donors (15). The safety of donation under such circumstances has predominantly been studied in Caucasians, and other races, especially African Americans, are at an increased risk for developing ESRD. Therefore it is reasonable to limit acceptance of hypertensive donors to well selected Caucasians.

Diabetes Mellitus

Subjects with diabetes or prediabetes or those at high risk for diabetes if living with single kidney may be at higher risk for developing diabetic nephropathy and may have faster progression of nephropathy. All donors should be evaluated with fasting blood glucose. Even if fasting sugars are not elevated, candidates with risk factors for diabetes—such as a first-degree relative with diabetes, gestational diabetes, or BMI >30—should undergo a glucose tolerance test or HgbA1c test (Table 4). Recently revised American Diabetes Association guidelines describe the use of these tests to diagnose diabetes and prediabetes (38). Candidates with prediabetes may not be appropriate for donation, especially in the presence of any other risk factors for diabetic nephropathy, including obesity, hypertension, or proteinuria. In the absence of any other risk factors, careful informed consent and adequate understanding by the candidate of potential risks must be confirmed.

Obesity

There is increasing recognition of the fact that obesity is associated with proteinuria and hypertension, and may lead to ESRD (39). Praga *et al.* showed that after uninephrectomy

Table 4. Diagnosis of prediabetes and diabetes

	Prediabetes	Diabetes
Fasting plasma glucose (mg/dl)	100–125	≥126
2-h plasma glucose with 75-g oral glucose tolerance test	140–199	≥200
HbA1C (%)	5.7–6.4	≥6.5
Reproduced with permission from the American Diabetes Association (38).		

for various diseases, those who were obese were dramatically more likely to develop proteinuria or renal dysfunction (40). BMI >30 also increases minor wound-related surgical complications from donor nephrectomy, although not major complications (41). A meta-analysis showed that most studies following obese donors were heterogeneous and had short follow-up, and that the two studies with somewhat longer follow-up (4 and 6 years) had conflicting results on GFR changes compared with nonobese donors (12). A more recent study showed that obese donors (BMI >30) are not at higher risk for reduced renal function compared with nonobese donors at a mean follow-up of 11 years. The authors found a higher incidence of hypertension and cardiovascular risk factors in obese donors, although this was similar to that found in a matched cohort from the NHANES (42). BMI >35 is considered a contraindication to donating by most centers (14), but factors such as muscle mass, body shape, and other risk factors should be considered in assessing the BMI. Overweight donors should be advised to lose weight before donating, and the potential risks of being overweight should be carefully discussed.

Proteinuria

Because proteinuria is potentially a sign of renal disease, a person with significant, persistent proteinuria should not be a donor. The main exception is orthostatic proteinuria, which can be diagnosed in those aged <30 years using a split urine collection (43). Transient proteinuria due to factors such as intensive exercise can be shown to be nonpathologic by repeat collections. Most US programs measure proteinuria using a 24-hour urine collection and use variable exclusion criteria, ranging from 150 mg to 300 mg daily (14). Many nephrologists advocate using albuminuria as an adjunct or better measure of glomerular abnormality, and 30 mg daily is a standard cut-off for albuminuria (44). Proteinuria >300 mg or albuminuria >30 mg would usually be an exclusion to donation, especially in the presence of any other risk factor for kidney disease.

Hematuria

Isolated hematuria may be urological (including stones or tumors) or glomerular. Imaging and cystoscopy address urological causes. For glomerular hematuria, a renal biopsy is required to distinguish IgA nephropathy and other causes of renal disease from normal histology. In a recent

study from Israel, asymptomatic, isolated, persistent microscopic hematuria in 16–25 year olds was associated with a low but increased rate of progression to ESRD (0.7% versus 0.045% in those without hematuria) over 20 years (45). Usually, a benign cause must be confirmed before accepting a donor with hematuria.

Nephrolithiasis

Recurrent nephrolithiasis after donation is a concern because it could lead to obstruction of the single kidney and may contribute to future renal dysfunction. However, high-resolution imaging performed on donors often identifies small, asymptomatic stones. A history of recurrent or multiple stones is usually a contraindication to donation. However, timed urine collections to look for metabolic risk factors for recurrent stones can help assess the risk of recurrent stones in borderline cases, such as those with ≤ 2 -mm calcifications on imaging, a remote history of stones or poor documentation that a prior episode of pain was due to stones. Contraindications for donation include struvite stones, cystinuria, and primary hyperoxaluria. Seventy-seven percent of US programs consider accepting donors with a history of stones (46).

Inherited Renal Diseases

A complete family history of kidney diseases, especially for the cause of renal failure in a genetically related recipient, is critical to the donor evaluation. For example, a strong family history of diabetic nephropathy is usually a contraindication to donation, especially in a young potential donor. In donors with a family history of polycystic kidney disease, ultrasound or computed tomography is highly sensitive in ruling out cystic disease, especially in those aged >30 years (47). In younger donors, polycystic kidney disease can only be ruled out by genetic testing; however, it requires identification of the specific mutation in the recipient.

Selection of donors is a complex process, and with the limited data available it is impossible to make exclusion criteria that are applicable to all donors. Hence, it is important to evaluate donors in totality and use the exclusion criteria in the context of other findings. Because younger donors are more likely to have time for any renal risk factors to lead to ESRD, we recommend being more stringent in their selection but would be more willing to accept healthy elderly donors with mild single abnormalities. Overall, the currently available data are reassuring for the short-term and long-term health of donors. However, there is a lack of long-term data for medically complex donors and we believe it is our responsibility to ensure that this gift is not to their detriment and that we give them accurate information about their risks. We support widespread and long-term follow-up of all living donors.

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Disclosures

None.

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