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Evaluation of high-risk living kidney donors

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1. ABSTRACT

Careful evaluation of potential living kidney donors is crucial to assure the well being of the donors, especially because they do not gain any direct medical benefit from donation. This process also helps assess the quality and safety of the organs donated to the recipients. While all programs share these goals, donor selection criteria vary significantly among U.S. transplant centers. In part, this is due to the limited data that exists as to long-term outcomes among donors who are medically complex, or at higher risk for complications, such as those with hypertension, obesity, or lower kidney function. This article reviews available evidence regarding outcomes after living donation and current trends in U.S. practices, and seeks to provide practical guidance in evaluating high-risk potential living kidney donors.

2. INTRODUCTION

Kidney transplantation is the preferred treatment for end-stage renal disease, and compared to deceased donor kidneys, living donor kidneys provide substantial graft and patient survival advantages to the recipients (1). In addition, there is an ever-increasing disparity between organ supply and demand, and living donor kidneys play an important role in meeting this demand. The advent of laparoscopic donor nephrectomy has reduced the morbidity of live donation (2), and increased public awareness of the need for live donors has also contributed to the substantial increase in living kidney donation since the first kidney transplant performed between identical twins in 1954. Finally, increasing evidence demonstrates the perioperative and long-term safety of donation, at least for young, healthy donors (3,4).

The evaluation of kidney donor candidates includes medical, surgical, immunologic, and psychosocial assessments. Suggested routine screening for a potential living kidney donor is summarized in Table 1.

Table 1. Routine screening for a potential living kidney donor

Blood testing - Biochemistry • Creatinine and blood urea nitrogen • Electrolytes • Liver function tests • Fasting plasma glucose • Fasting lipid profile • PSA (if indicated) • Pregnancy test (if indicated)
Blood testing - Hematology • Complete blood count • Coagulation profile
Blood testing - Viral serologies • Hepatitis B and C • HIV 1 and 2 • Epstein-Barr virus • Cytomegalovirus • Syphilis • Toxoplasma
Urine testing • Dipstick for glucose, protein, and blood • Microscopy and culture • Measurement of glomerular filtration rate • Measurement of protein excretion rate
Cardiopulmonary testing • Chest X-ray • Electrocardiogram • Stress test (if indicated) • Echocardiogram (if indicated)
Renal imaging • CT scan of the kidneys and urinary system

While there is some consensus about the components of the living donor evaluation, there are no universal criteria used to exclude potential donors. The factors that have increased the numbers of donors, including the benefits to recipients and reassurance to donors, have contributed to the loosening of exclusion criteria over the last 15-20 years. The acceptance of more medically complex donors is documented both in the United Network for Organ Sharing (UNOS) data (5), and in surveys of transplant centers in the U.S. (6). For example, programs have increased their acceptance of genetically unrelated donors and no longer have an upper age limit for donation. While data evaluating the safety of accepting more medically complex donors is limited, here we review the evidence that is available, and attempt to provide guidance in evaluating high-risk potential living donors.

3. RISKS OF LIVING KIDNEY DONATION

3.1. Perioperative risks

Data from the UNOS from 1994 to 2009 showed that surgical mortality within 90 days of living kidney donation was 3.1 per 10,000 donors (7). This risk is lower than that of non-donor nephrectomy (approximately 260 per 10,000 cases) (8) or laparoscopic cholecystectomy (approximately 18 per 10,000 cases) (9).

The risk of major morbidity related to donor nephrectomy is small (2-5%). Reported perioperative complications include bleeding, internal organ injury, lymphocele, urine leak, ileus, pneumothorax or pleural effusion, atelectasis, pneumonia, urinary tract infection, deep vein thrombosis or pulmonary embolus, as well as wound complication such as wound rupture, wound infection, and incisional hernia (10,11).

3.2. Long-term risks

Long-term risks after donor nephrectomy have been shown to be minimal (3,4). However, the most prominent long-term follow-up studies of living donors were performed in Minnesota and Switzerland, and addressed outcomes in carefully selected, young, Caucasian donors. Whether this reassuring data applies to higher risk donors, such as those with hypertension or African American ancestry, is still unknown.

There are several studies looking at renal function after kidney donation. A meta-analysis of the studies that examined the long-term effect of reduced renal mass after unilateral nephrectomy from various causes (60.5% from organ donation) showed the average decrement in glomerular filtration rate (GFR) of 17.1 mL/min and the subsequent improvement with each 10 years of follow-up (1.4 mL/min/decade; 0.3-2.4. mL/min/decade) (12). The authors concluded that, in normal individuals, unilateral nephrectomy did not cause progressive renal dysfunction. A similar decrease in GFR after donation was also demonstrated in a study from University of Minnesota showing an average remaining estimated GFR of 76% of the estimated GFR at the time of donation (4). Moreover, this study suggested that a younger age and a higher estimated GFR at the time of donation, as well as a longer time since donation were associated with

a greater compensatory increase in the estimated GFR in the remaining kidney.

In the general population, proteinuria is a marker of kidney disease and is associated with progression of renal failure, along with worse cardiovascular outcomes and mortality (13,14). For the kidney donor population, a systemic review of 42 studies quantified proteinuria after kidney donation (a total of 4,793 donors), with an average of 7 years (range 2-25 years) of follow-up. This study showed substantial differences in the reported incidence of proteinuria after donation, from less than 5% to more than 20% (15). The pooled incidence of proteinuria was calculated to be 12% (95% confidential interval of 8-16%). Whether the development of proteinuria in the donor population could contribute to the development or progression of kidney disease after donor nephrectomy remains unclear, since most available data suggests that the initial decrement in GFR is generally not followed by an accelerated decline.

The risk of developing hypertension after kidney donation also remains uncertain. There are several reports on blood pressure after kidney donation, but the results have been somewhat conflicting. Although several studies reported an increase in blood pressure of 5-10 mmHg (16-20), others found no increase (21,22). A meta-analysis was performed and included 48 studies from 28 countries (a total of 5,145 donors) (23). In this analysis, blood pressure from controlled studies with at least 5 years of average follow-up was 5 mmHg higher in donors than in control participants. An increased risk for hypertension was noted in one out of the 6 controlled studies with the relative risk of 1.9 (95% confidential interval of 1.1-3.5) (24). However, most studies were retrospective, did not have control groups, and had significant rates of incomplete follow-up. The largest single follow-up study of former living donors does not suggest an increased risk of hypertension (4).

A retrospective cohort study using UNOS data from 2004 to 2005 reported a significantly varied proportion of medically complex donors (defined as ones with hypertension, obesity, or estimated GFR less than 60 mL/min/1.7.3m^2) among transplant centers in the U.S., ranging from 0% to 65% (mean of 24%) (25). This substantial variation in protocols and criteria for living kidney donors reflects a lack of good evidence regarding postdonation outcomes in these medically complex donors. The following topics will focus on these issues in medically complex and racially diverse donors.

4. HIGH-RISK LIVING KIDNEY DONORS

4.1. Age

Older donors are more likely to have comorbidities or medically complex issues such as hypertension and lower kidney function. So not surprisingly, they tend to have greater postoperative mortality (7). However, older donors have fewer years at risk to develop chronic kidney disease, so a risk factor such as hypertension is less likely to lead to end-stage renal disease than in a younger donor (26).

UNOS data as well as a survey of U.S. transplant center policies in 2007 show a trend toward increased acceptance of older donors (5). Fifty-nine percent of responders in this survey had no upper age limit, compared to only 27% from an earlier survey in 1995 (6,27).

4.2. Race

In the general population, African Americans have substantially higher rates of chronic kidney disease and end-stage renal disease compared to other ethnic groups (28). However, it is uncertain whether kidney donation increases future risk of hypertension and kidney disease in African Americans more than it does in Caucasians. Several studies have suggested that the risk of end-stage renal disease is increased in black donors compared with white donors (29,30). However, these increased relative risks are not greater than in the general population of blacks compared to whites, suggesting that living donation does not carry significantly greater risks for blacks compared to whites. For example, Cherikh *et al* showed that even though the rate of end-stage renal disease was nearly five times higher for blacks than for whites, these ethnic differences were similar to those previously reported for end-stage renal disease in the general population (31). Another matched cohort showed long-term mortality risk was not higher for kidney donors than for matched NHANES III participants for all patients and also when stratified by age, sex, and race (7).

Recently, high-risk variants of the APOL1 gene have been found to confer a markedly increased risk for hypertension-attributed kidney disease, focal segmental glomerulosclerosis, and HIV nephropathy in African Americans (32). The high-risk genotype in deceased donor kidneys

also appears to be associated with worse allograft survival in recipients (33), although the high-risk genotype in recipients themselves does not seem to affect allograft survival (34). Because of increased concerns about outcomes in African American donors, APOL1 genotyping in African Americans who are potential donors holds promise for identifying subsets of African Americans at higher or lower risk for adverse outcomes. However, the impact of APOL1 variants on future kidney-related outcomes in carefully screened living kidney donors with African heritage is currently unknown.

4.3. Obesity

Obesity in the general population has been associated with surgical complications and other long-term medical problems such as diabetes mellitus, hypertension, dyslipidemia, sleep apnea, liver disease, and cardiovascular disease. Obesity is also associated with proteinuria, chronic kidney disease, and end-stage renal disease (35-38). However, limited data exists regarding the effect of obesity on outcomes after donor nephrectomy. Praga *et al* showed that obese patients undergoing uninephrectomy for medical reasons, not donation, were at high risk for developing proteinuria and renal dysfunction (39). However, Tavakol *et al* found that obese donors were not at higher risk for long-term renal function impairment compared with non-obese donors at a mean follow-up of 11 years. The authors also suggested that the increased incidence of hypertension and other cardiovascular disease risk factors in these obese donors was due to their obesity and was not further exacerbated by nephrectomy, as the incidence was similar to that found in a matched cohort from the NHANES database (40).

There is encouraging evidence that laparoscopic donor nephrectomy is generally safe in selected obese donors and does not result in a high rate of major perioperative complications (41). Those donors with high body mass index (BMI) had slightly longer operative time and minor wound complications.

Factors that should also be considered along with BMI include body shape, waist circumference, and lean muscle mass. Since these variables are less carefully studied than BMI, they are rarely used in isolation, but can be considered in candidates with borderline BMI, for example, to accept as donor someone who is highly muscular. Obese and overweight potential donors should be encouraged to lose weight prior to kidney donation, evaluated carefully, and informed of both perioperative and long-term risks.

4.4. Hypertension

Accurate measurement of blood pressure is crucial. At least two measurements should be made and the results confirmed on an additional visit (42). Because as many as 20-35% of patients diagnosed with hypertension have a white-coat effect (43), ambulatory blood pressure monitoring should be considered for potential donors with isolated elevated blood pressure. A recent small study of 17 donors showed remarkable differences between clinic systolic blood pressure and ambulatory systolic blood pressure prior to donation. These differences disappeared 6 months after donation, suggesting a substantial white-coat effect on systolic blood pressure associated with living kidney donor evaluation (44).

Limited data exists on long-term outcomes after live kidney donation by hypertensive donors, and even less information regarding non-Caucasian populations. Textor *et al* compared donors with preexisting hypertension to normotensive donors and found no increase in blood pressure or differences in renal function or urinary protein excretion (45). Tent *et al* reported similar results, also in a mostly Caucasian population (46).

Hypertension exclusion criteria of U.S. transplant centers seem to have become more flexible based on the surveys in 1995 and 2007 (6,27). More recently, close to half of programs will consider donors taking antihypertensive medications. Factors that potentially make the exclusion criteria for preexisting hypertensive donors stricter include younger age, and African American or Hispanic ethnicity. We also suggest that hypertensive donors only be accepted if end-organ damage is ruled out by echocardiogram, urinalysis, and fundoscopy.

4.5. Prediabetes and risk factors for diabetes mellitus

Diabetes mellitus is generally associated with an increased risk of postsurgical complications and future development of renal failure compared to the general population. A study done by Silveiro *et al* suggested that nephrectomy in patients with type 2 diabetes mellitus was associated with the increased prevalence of microalbuminuria after nephrectomy and might increase the disease progression (47). The guideline from the International Amsterdam Forum on the living donor care advised against

donation from individuals with a history of diabetes mellitus, fasting blood glucose ≥126 mg/dL on at least two occasions, or two-hour glucose on an oral glucose tolerance test or OGTT ≥200 mg/dL) (48). More recent recommendations by the American Diabetes Association also suggest that HbA1c ≥6.5 is diagnostic of diabetes.

Most U.S. transplant centers regard established diabetes mellitus as a contraindication to living kidney donation and many centers also exclude individuals at high risk (6). Risk factors for developing diabetes mellitus include glucose elevations to the pre-diabetes range (HbA1c 5.7-6.4), impaired fasting glucose (100-125 mg/dL), and impaired glucose tolerance (140-200 mg/dL at two hours after OGTT). Other risk factors to consider include an elevated BMI, a history of gestational diabetes, and a familial history of diabetes, especially among first-degree relatives of diabetics (49).

4.6. Kidney function

All potential kidney donors should have their kidney function measured to ensure that they have adequate GFR, both for themselves and for their recipients after transplantation. The Amsterdam Forum suggested that a GFR less than 80 ml/min or two standard deviations below normal (based on age, gender, and body surface area corrected to 1.73 m^2) generally preclude donation (48). This guideline is partly based on the finding that kidneys from donors with GFR less than 80 ml/min are associated with a relative risk of graft loss of 2.28 compared to those with higher GFR (50). However, to protect long-term donor safety, we recommend using higher GFR exclusion criteria in younger donors than older donors. While 80 ml/min/1.73 m^2 is a reasonable GFR for a 60-year-old donor with relatively fewer years during which GFR might decline, the same GFR of 80 ml/min/1.73 m^2 in a 25-year-old donor should raise concerns as to why that donor's kidney function is so much lower than average for his/her age, and raise concerns that a decline in renal function over time might result in end-stage renal disease.

Creatinine-based estimations of GFR using the Modification of Diet in Renal Disease, Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration, and other equations are inaccurate for subjects with close to normal kidney function, especially in obese donors (51-53). These equations tend to underestimate GFR, and the higher the GFR, the more the equations deviate from measured GFR, both above and below the true value. Most transplant centers in the U.S. measure kidney function using a 24-hour urine collection for creatinine clearance. To assess for over or undercollection of urine, women should have 15-20 mg/kg body weight creatinine and men 20-25 mg/kg body weight (54). Often a second collection is required if the initial collection is not adequate. Some programs are able to use a direct measurement of GFR using an iodinated or radiolabeled marker for all donors (6), while others reserve these direct measures for donors with inconsistent or unexplainable creatinine clearance measurements.

4.7. Proteinuria

Proteinuria is one of the hallmarks of kidney disease, which should be evaluated as a part of the standard donor work-up. Even though the normal laboratory values can vary, the Amsterdam Forum suggests that 24-hour urine protein of more than 300 mg/day is a contraindication to donation (48). Most U.S. transplant centers quantify protein using a 24-hour urine collection. About 60% of centers use a cut-off urine protein of 300 mg/day while 36% of centers use 150 mg/day (6). The main exception to these exclusion criteria is orthostatic proteinuria, a benign condition that can be diagnosed in those under 30 years old using a split urine collection (55).

Urine albumin testing has been shown to be more sensitive than urinary total protein to detect kidney disease, not only for diabetic nephropathy but also for non-diabetic kidney diseases (56). While its value in the kidney donor evaluation has not been directly studied, extensive data suggests an increased risk of developing kidney disease with albumin excretion greater than 30 mg/g creatinine (57). Some suggest that kidney donors be screened and followed with urine albumin measurement, and that candidates with mildly elevated total protein excretion (24-hour urine protein of 150-300 mg) but normal albumin excretion not be excluded from donation (58).

Other factors should also be considered in the setting of borderline proteinuria. For example, transient proteinuria can be benign if associated with fever or exertion. The presence of any other risk factors for kidney disease should be taken into consideration such as concomitant hematuria, prediabetes, hypertension, obesity, or smoking.

4.8. Isolated hematuria

A recent large study of over one million Israeli adolescents and young adults suggested

that patients with persistent asymptomatic isolated microscopic hematuria were at an increased risk of developing end-stage renal disease during a mean follow-up of 22 years, although the incidence and absolute risk remained quite low (0.7% compared with 0.045% in the control group) (59). Moreover, the subjects also developed end-stage renal disease at a younger age, with disease more likely due to primary glomerular diseases (incidence rate of 19.6 compared with 0.55 per 100,000 person-years in the control group). Therefore throughout investigation in donors with hematuria is warranted.

Urine cytology and complete urologic work-up should be considered in potential donors with persistent microscopic hematuria to exclude urological malignancy and stone disease. Persistent isolated microscopic hematuria could be due to glomerular causes, predominantly IgA nephropathy, Alport syndrome, and thin basement membrane disease. IgA nephropathy and Alport syndrome are well known to cause renal failure, and renal biopsy is required to distinguish these conditions from benign hematuria with normal renal histology. Some controversy exists as to whether thin basement membrane disease is a contraindication to donation, as many consider thin basement membrane disease to be benign, but some studies have suggested otherwise (60,61). Before allowing someone with thin basement membrane disease to donate, a careful informed consent discussion should highlight the potentially increased risk of developing future kidney disease.

4.9. Nephrolithiasis

The major concern for donors with urinary tract stones is that they could recur and might cause obstruction of a solitary kidney. Some population studies have also found symptomatic kidney stone formers to be at increased risk for chronic kidney disease, especially among those with rare hereditary diseases (cystinuria, primary hyperoxaluria, Dent disease, and 2,8-dihydroxyadenine stones), recurrent urinary tract infections, struvite stones, hypertension, and diabetes mellitus (62). Age of the donor is another important factor since younger donors have a longer exposure to the risk of stone recurrence or renal insufficiency. However, kidney transplantations have been successfully performed from donors with stones (63-65). Ex-vivo ureteroscopy is a technically feasible means of rendering a stone-bearing kidney stone free, without compromising ureteral integrity or kidney allograft function (66,67).

The guideline from the International Amsterdam Forum on the living donor care suggested that stone formers who should not donate are those with nephrocalcinosis on X-ray or bilateral stone disease, as well as those with stone types that have high recurrence rates and are difficult to prevent (48). These stones include cystine stones that have a high rate of recurrence and a need for urologic procedures in the donor, struvite stones or infection stones that are difficult to eradicate, stones associated with inherited or other systemic disorders (such as primary or enteric hyperoxaluria, distal renal tubular acidosis, and sarcoidosis), stones in the setting of inflammatory bowel disease, and other recurrent stones despite being on appropriate treatment.

However, a candidate with a remote history of kidney stones who does not have stones found on high resolution computed tomography may be able to donate a kidney, and would be accepted at most U.S. transplant programs (68). Screening for metabolic stone forming abnormalities, including timed urine collections, can also be helpful in assessing the risk of stone recurrence, especially in a borderline candidate.

4.10. Familial kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease leading to end-stage renal disease in adults (69,70). Since the main goal of screening the potential living related kidney donors is to exclude the possibility of the donors developing the disease in the future, an ideal screening test should have a negative predictive value (NPV) of 100%.

Ultrasound has demonstrated a NPV of close to 100% when used to screen individuals with a family history of ADPKD who are older than 30-40 years old (71,72). However, ultrasound screening for those donors who are younger than 30-40 years old, especially with milder disease including type 2 ADPKD, is much less accurate, with NPV ranging from 85% to 97%. Computed tomography and magnetic resonance imaging are somewhat more sensitive (73,74), but the younger the candidate, the less sensitive will be the imaging.

Younger donor candidates require genetic testing by direct mutational analysis that is commercially available for ADPKD. Accurate genetic testing requires knowledge of the specific mutation causing ADPKD in the family, but this is easily determined in the typical scenario in which a subject wishes to donate to a

family member with end-stage renal disease from ADPKD.

5. SUMMARY

The living kidney donor evaluation can be a complicated process, especially for medically complex donors. Lack of long-term evidence makes it difficult to make evidence-based recommendations in many cases. In these situations, clinicians should make individualized decisions for each potential donor. Many exclusion criteria for donation involve numerical cut-offs, but it is very important that they not be applied rigidly, without considering other aspects of the evaluation. All of the risk factors should be assessed together, in order to estimate the composite perioperative and long-term risk to the donor. Overall, current evidence regarding outcomes of kidney donors is reassuring, even though there is limited long-term data for medically complex donors. We believe that long-term follow-up is necessary for all living donors, not only for their individual health, but also for data collection to make better recommendations in the future.

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