Do Living Kidney Donors Have CKD?

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Living kidney donor transplantation is an increasingly used treatment for end-stage renal disease because it both confers excellent outcomes to transplant recipients, and is considered a safe procedure for prospective donors. The short- and long-term safety of prospective donors is paramount to the continued success of living donation. Although the initial experience with living kidney donors mostly included the healthiest donors, increasing need for organs and secular trends in the general population have subtly reshaped prevailing suitability criteria for donation. As the practice of living donation evolved over time, our understanding of kidney disease has also changed as we embraced the framework of the K-DOQI guidelines. It is not uncommon for donors to fit into some of the K-DOQI guidelines paradigms of risk and disease; however, whether there is a true biological consequence or whether it is a merely semantic conundrum remains unclear. Regardless, this is an important issue, and therefore future efforts should aim at addressing this matter.

Key Words: Kidney disease, Living donor, GFR

Living kidney donation allows for a planned transplantation process and provides better clinical outcomes when compared with those of deceased donors. The continuously increasing demand for organs and the changing demographics of the living kidney donor population have been subtly reshaping concepts of donor suitability, with more lenient clinical criteria of acceptance.[1-4]

Three current issues for living donors are their increasing age at donation, selected acceptance with isolated medical abnormalities, and renal function outcomes and consequences that may include CKD.[5] Also of note is the increasing rate of living donation among African Americans, who in the general population are known to be at increased risk for hypertension, hypertensive nephrosclerosis, and ESRD.[6] Furthermore, some renal transplantation programs allow selected hypertensive individuals to donate a kidney.[7] Given these developments, accurate assessment of kidney function in the living donor is critical, with the need to (1) establish an appropriate threshold for acceptance of a donor and (2) determine long-term functional outcomes. An unintended consequence of living kidney donation could be having a donor being labeled with stage 3 CKD according to current recommendations by the NKF.[8,9] However, the correct interpretation of the direct applicability of this staging among former living donors is debatable, and it is being challenged.[10-14]

Unlike any other situation in the practice of medicine, living kidney donors undergo extensive evaluation, with the express and central goal of confirming suspected health instead of suspected disease. Because living donation is an elective procedure, with no direct physical benefit to the donor, it is essential that the evaluation process carefully assess predonation kidney function taking into perspective the factors that may potentially affect postnephrectomy glomerular filtration rate (GFR). Interpreting whether predonation GFR will adequately provide sufficient and acceptable residual postnephrectomy GFR to the donor and sufficient GFR to the recipient is challenging but crucial to a successful transplant procedure.

According to current recommendations, living donors should have a GFR of ≥80 mL/min or, alternatively, a kidney function level within 2 standard deviations of normal for age and gender.[1,2,4] Although these recommendations do not clearly specify the method for renal function assessment, most centers perform this critical step using timed urine collections for creatinine clearance. Others rely on more precise and accurate techniques, such as exogenous marker clearances. Nevertheless, no standardized reference values exist for each of the procedures used in clinical practice. Thus, the decision of proceeding (or not) with donation is unfortunately often a matter of subjective interpretation rather than more precise science. Because of the emphasis placed by the NKF on GFR to determine the state of renal health versus disease, renal function assumes an even greater role in understanding living donor outcomes.

Predonation Evaluation of Kidney Function

Traditionally, GFR has been considered the best overall marker of kidney function.[15] In clinical practice, other than living kidney donor evaluation, GFR is commonly inferred by either the interpretation of serum creatinine levels or by the use of creatinine-based GFR estimation equations.[8,16,17] It is clear that the creatinine-based GFR estimation equations are not acceptable in the setting of living donor evaluation, mostly because a significant percentage of kidney function needs to be lost before there is a corresponding change in serum creatinine level. However, although serum creatinine alone is not a sensitive marker of kidney dysfunction, it is a specific marker of

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kidney disease.[18] For example, if a prospective donor has a serum creatinine level elevated more than normal values during the evaluation process, he/she is likely to have kidney disease, and therefore the serum creatinine could be used for initial screening of interested prospective donors.

The urine creatinine clearance has traditionally been the method of choice to study kidney function in potential donors. Two clearances are usually done to minimize methodological errors. Although the creatinine clearance always overestimates true GFR because of the tubular secretion of creatinine, in conjunction with a comprehensive laboratory and medical evaluation, this method has become the "standard of care" across most transplant centers mostly owing to the lack of a better alternative. This is a good approach as long as the clinician keeps in mind the common potential limitations of this test: (1) it is reliable only when done properly, (2) it overestimates GFR by an unpredictable percentage, and (3) it is not usually interpreted in the context of age- and gender-specific reference values. To exemplify each of these points, consider a potential kidney donor who has 2 urinary creatinine clearance rates (point 1) that average to 87 mL/min and allow donation. This average creatinine clearance may actually reflect a GFR of >80 mL/min/1.73 m^2 (point 2). Although this value may be normal for a 55-year-old female donor, it may not be for a 25-year-old male donor (point 3). Therefore, extreme caution should be exercised with this approach.

CLINICAL SUMMARY

- Kidney function assessment is a critical aspect of the donor evaluation process, but the obtained information should always be interpreted in the context of other clinical and laboratory data. This is also true when assessing kidney function post-donation.
- Kidney donors have an obligate numerical reduction in glomerular filtration rate that rarely progresses to ESRD. In the absence of progressive renal dysfunction, proteinuria or hypertension, this mere reduction in GFR among living kidney donors should not be interpreted as connoting CKD.
- Registry data have shown that even among groups at high risk for kidney disease such as African Americans, ESRD rates among former living donors is no higher than that observed in the general population. Unfortunately, outcomes data are obtained from retrospective studies, studies with no appropriate controls, and registry studies.
- Future studies of living donor outcomes should include prospective follow up of former donors with capture of biologically relevant measures of cardiovascular, metabolic, and renal parameters.

Assessment of GFR by clearances of exogenous markers is the "gold standard" approach. Their use in living kidney donors could be considered one of the most clinically valuable applications of these methods.[19,20] However, these methods are also not exempt from methodological variability and are expensive, but they are more consistent and reliable. Currently, donor renal function is often evaluated without taking into consideration age- and gender-specific reference values, with the result that any value >80 mL/min/1.73 m^2 is generally considered appropriate for proceeding with donation. Although long-term follow-up has demonstrated that former kidney donors have similar or better life expectancy and lower risk of ESRD than the general population,[21-23] a small number of kidney donors have developed the need for renal replacement therapy.[24] This outcome might be unavoidable in some because of new and unpredictable kidney disease; however, it is not clear whether subjects with prenephrectomy GFR >80 mL/min/1.73 m^2, but in the lower percentiles of normal based on age and gender reference values (ie, abnormal or suboptimal), are indeed at higher risk for poor renal outcomes.

Postnephrectomy GFR and Determinants of Kidney Function Compensation

Donor nephrectomy represents the abrupt loss of approximately 50% of nephron mass, with an immediate and corresponding decrease in GFR. However, the remaining contralateral healthy renal parenchyma has the ability to recover a significant percentage of lost function within a relatively short time. Several investigators have shown that in healthy individuals, unilateral nephrectomy is followed by a compensatory increase in functional capacity of the contralateral kidney by approximately 20% to 40%.[25-29] Velosa and colleagues,[28] among others, showed that as early as 1 week after nephrectomy, renal function has recovered to levels slightly lower than those achieved at 6 months after nephrectomy. Similarly, others showed that the GFR at 1 year after donation was essentially the same or slightly improved from the one achieved as early as 1 week after donation.[25,30]

The mechanisms underlying this "adaptive hyperfiltration" are complex and likely determined by several factors.[27] Demographic and anthropometric factors associated with GFR compensation after nephrectomy include age, gender, race, and body size. The relationship between GFR and aging has been a matter of investigation. Although an invariable decrement in GFR occurs as humans age, when exactly this physiological process becomes a pathological one is debatable.[27,31-34] Several investigators hypothesized that kidneys from older donors could have a decreased "renal reserve capacity" that would manifest as impaired kidney function after donation. Studies by Velosa and colleagues as well as by Saxena and colleagues, among others, showed that