

Reassessing Medical Risk in Living Kidney Donors

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ABSTRACT

The short- and long-term effects of unilateral nephrectomy on living donors have been important considerations for 60 years. Short-term risk is well established (0.03% mortality and <1% risk of major morbidity), but characterization of long-term risk is evolving. Relative to the general population, risk of mortality, ESRD, hypertension, proteinuria, and cardiovascular disease is comparable or lower. However, new studies comparing previous donors with equally healthy controls indicate increased risk of metabolic derangements (particularly involving calcium homeostasis), renal failure, and possibly, mortality. We discuss how these results should be interpreted and their influence on the practice of living donor kidney transplantation.

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A kidney transplant from a living donor—ideally performed as the initial modality of RRT—provides the best outcome for a patient with ESRD.¹ However, because the donor must undergo a medically unnecessary procedure, concern for donor safety has always been part of the process. Since its origins 60 years ago, the enduring acceptance of living donor transplantation has been based on a combination of excellent recipient outcomes and evolving understanding of the original observation by Murray² that, in actuarial terms, there was no increased risk of living with one kidney.

Early studies documented what became accepted as relatively low surgical risk (0.03% mortality and <1% major morbidity) with rapid compensatory increase in GFR in the remaining kidney.³ In the last two decades, long-term follow-up studies (some over 30 years; both single center and registry data) from Europe, Asia, and the United States showed no increased risk for donors compared with the general population.^{4–6} Major findings included that donors (1) lived as long (or longer) as the general population, (2)

had a relatively stable GFR over many years without increased rates of ESRD, (3) had similar risks of hypertension and proteinuria as nondonors, and (4) had excellent quality of life. The first iteration of United Network for Organ Sharing regulations addressing living donor evaluation and consent processes in 2013 reflected these findings.⁷ Similarly, both the 2002 Kidney Disease Outcomes Quality Initiative and 2012 Kidney Disease Improving Global Outcomes guidelines on CKD acknowledged the paucity of evidence that reduced GFR as a consequence of donor nephrectomy was associated with increased risk of morbidity or mortality.^{8,9}

A limitation of these previous studies, however, is that donors derive from a highly selected group of healthy individuals and not the general population; the ideal control subject would be equally as healthy as a donor at the time of nephrectomy. With maturing of several granular public health databases (including the National Health and Nutrition Examination Surveys [NHANES]), it is now possible to identify such controls.¹⁰ Indeed, Ibrahim *et al.*⁵ used NHANES controls matched for age,

sex, race or ethnicity, and body mass index in the 2009 Minnesota study. Another major study using matched registry data documented equal mortality risk between previous donors and selected controls, albeit over a relatively short median follow-up of 6.5 years.¹¹

Several important new reports, all using controls with health status comparable to donors at the onset of observation, have now further expanded our understanding of donor risk. In a prospective evaluation of living donors ($n=201$) and matched healthy concurrent controls ($n=198$) at eight centers, Kasiske *et al.*¹² reported mean GFR 6 months postdonation as 68 ± 10 ml/min per 1.73 m² that was accompanied by significant alteration in the calcium/phosphorus/parathyroid axis. Donor Nephrectomy Outcomes Research (DONOR) Network investigators, in a cross-sectional study of 198 previous donors, documented similar changes plus increased fibroblast growth factor 23 levels.¹³ More recently, two large registry-based studies report previously undocumented incremental long-term risk of ESRD and, possibly, mortality in prior donors. Mjoen *et al.*,¹⁴ using Norwegian data with a median follow-up of 15.1 years, reported relative risk for ESRD of 11.38 (95% confidence interval [95% CI], 4.4 to 29.6) and relative

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mortality risk among donors of 1.3 (95% CI, 1.1 to 1.5). In the United States, a comparison (using Center for Medicaid and Medicare Services [CMS] data) of 80,347 former donors with matched NHANES controls showed no difference in mortality over 6.3 (3.2–9.8) years.¹⁵ The same group, again using CMS data but with a median follow-up of 7.6 years (maximum of 15 years), compared risk of ESRD in 96,217 donors with matched NHANESIII controls and documented a similar magnitude (to the Norwegian study) of increased ESRD risk in donors: 30.8/10,000 (95% CI, 24.3 to 38.5) in previous donors versus 3.9/10,000 (95% CI, 0.8 to 8.9) in healthy controls.¹⁶ Application of Kaplan–Meier methods allowed estimation of lifetime risk of ESRD as 326/10,000 in the general population, 90/10,000 in previous donors, and 14/10,000 in healthy nondonors.

Without question, each of these studies has limitations. The long-term implications of short-term changes in calcium or uric acid homeostasis in patients with stable renal function and no significant albuminuria are uncertain. As Gill and Tonelli¹⁷ noted editorially, there are clear statistical challenges inherent in population-based studies with a small number of end points in both donor and control cohorts that threaten generalizability. In the Norwegian study, all of the controls were from a small, ethnically homogenous county (Nord-Trøndelag) in rural Norway, where life expectancy exceeds national norms.¹⁸ Is this control population suitable for Norwegian donors; is it generalizable globally? Eighty percent of the Norwegian donors were first-degree relatives of the recipients. Similarly, Muzaale *et al.*¹⁶ report that 84% of those who developed ESRD were among the 70% of donors noted to be biologically related, although the ESRD incidence of 34.1/10,000 (95% CI, 26.9 to 43.3) in relatives was not statistically different from the ESRD incidence of 15.1/10,000 (95% CI, 8.7 to 26.3) reported in nonrelated donors ($P=0.15$).¹⁶ Although perhaps best quantitated in first-degree relatives of patients with diabetes with nephropathy (risk at least 2–2.5 times greater), it is widely accepted that persons biologically related to patients with CKD are at greater

risk for ESRD than those with no family history.¹⁹

Apart from any limitations, however, many of the findings are consistent with our evolving understanding of progressive kidney disease. Muzaale *et al.*¹⁶ found ESRD to most likely afflict older men of minority descent, characteristics (age, gender, ethnicity) already recognized as risk factors. Similar to data published by Lentine *et al.*,²⁰ black donors and nondonors alike were at greater risk for ESRD than white donors. The concepts of age at evaluation for donor nephrectomy and time at risk after donation are emphasized in the work of Steiner *et al.*,²¹ which notes that most ESRD (in the United States) begins after 60 years of age. Thus, current data (like the data in the work by Muzaale *et al.*¹⁶ with a mean donor age of 40.2 ± 11.1 years, and maximum follow-up of 15 years) do not include many of those at greatest risk and therefore, underestimate overall propensity for ESRD.²¹ Ultimately, Steiner *et al.*²¹ suggest that long-term renal risk after donor nephrectomy will recapitulate the demographics of risk in the general population: it will increase with age and have greater effect in minority populations.⁷ If, indeed, this interpretation is valid, our ability at the time of donor evaluation to define lifetime risk for an individual is limited, a factor that already influences our discussion and decision making, particularly with younger and minority donor candidates.

The newer data also offer some reassurance and enhance our ability to have critical conversations with potential donors. The works by Kasiske *et al.*¹² and the DONOR Network investigators¹³ document preservation of renal function without significant proteinuria in the overwhelming majority of previous donors. Additionally, regardless of hazard ratios or cohort characteristics, the incidence of ESRD and mortality among previous donors is very low over very lengthy periods of time. In the Norwegian study, 0.47% of donors (all Caucasian) developed ESRD over 15.1 (1.5–43.9) years (nine total donors with ESRD; all were family members of recipients, seven of whom had immunologic renal diseases likely to have affected both kidneys).¹⁴ In the study by Muzaale *et al.*,¹⁶

99 (0.1%) of 96,217 donors studied developed ESRD after 7.6 years (interquartile range, 3.9–11.5 years); estimated lifetime risk of ESRD for all donors was 0.9%, which is less than the 3% risk for the general population but greater than the 0.14% risk in healthy nondonors.

Beyond caution and reassurance, and after six decades of concern for living donor welfare, how are the nephrology and transplant communities to deal constructively with these recent publications? First, the notion that living donors must accept risk at some level is not novel; we and we suspect most of those involved in living donor transplantation have generally tried to communicate this fact to prospective donors throughout our careers. The recent codification by the United Network for Organ Sharing of standards for evaluation and informed consent in potential living donors reflects acceptance of the primacy of these concerns and requires their implementation at each transplant center.⁷ Second, these reports clearly advance and refine our understanding of medical risk in living donors. Certainly, maturing of the databases examined by Kasiske *et al.*¹² and the DONOR Network¹³ should result in additional insight into physiologic and potentially pathophysiologic consequences of donor nephrectomy. Third, payers and regulators alike must understand these data as a work in progress, requiring the same perspicuity in interpretation as we practitioners ought to practice; rash decisions on the basis of superficial reading of evolving data are never justified. As has been the evolutionary norm since the original observations by Murray,² additional studies must and will be performed, with findings that will further refine our understanding of long-term donor risk and expand the evidence base necessary to support informed policymaking. Fourth, we must not conflate the issue of studying long-term risk of donor nephrectomy with ensuring that all transplant centers adhere to the highest standards of evaluation and donor care. Centers must be held responsible for implementation of standards that promote optimal donor outcomes in the perioperative and early postoperative

periods. However, it is unrealistic to expect all transplant centers to maintain extended contact with previous donors sufficient to address the issues raised in these new reports.²²

Finally, appropriate informed consent on the part of a potential donor remains at the core of the process. Though possibly perceived as challenging old assumptions regarding donor risk, the new data, rather, amplify our ability to communicate with candidates throughout the donor process. Assessment of risk and benefit for living donors has always occurred against a backdrop of complex interactions that cannot be reduced to either pure paternalism or unrestrained autonomy.²³ Provision of accurate information before nephrectomy and advocacy for health maintenance after nephrectomy reflect our core commitment to donors. While awaiting ultimate determination of long-term medical risk through data from newer studies that will confirm, expand, or refute the current data, the twin cores of transparency and trust must remain intact.

DISCLOSURES

None.

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