Debate: PRO Position

Formal Assessment of Donor Kidney Function Should Be Mandatory

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The most reliable measure of overall kidney function is the glomerular filtration rate (GFR). Whether living kidney donors should undergo determination of GFR using the urinary clearance of a true filtration marker (e.g. inulin, iothalamate or iothexol) is a subject of debate. Among the disadvantages is the burden of a prolonged and laborious, but relatively costly procedure. Currently, only small fractions of academic centers determine true GFR in kidney donors. Most transplant centers use either a 24-hour urinary creatinine clearance, or a serum creatinine-based regression equation to estimate GFR (eGFR) in the evaluation of potential donors. Traditionally, a level of GFR <80 ml/min/1.73 m² is the threshold below which living donors are rejected. The rationale for this threshold is somewhat arbitrary but reasonable. In our laboratory a true GFR (inulin clearance) of 80 ml/min/1.73 m² represents only the sixth percentile in a large population of healthy volunteer adults below the age of 50 years. Because of tubular creatinine secretion, substituting a creatinine clearance of 80 ml/min/1.73 m² to define the threshold, will often lead to inclusion of donors whose true GFR is <80 ml/min/1.73 m².

Living kidney donation is one of the few areas of modern medicine in which an exception has been made to the notion of *primum non nocere* (first, do no harm), the foundation of the Hippocratic Oath and a guidepost of medical ethics. Live kidney donation is widely considered

an altruistic act to enhance longevity and quality of life for a loved one with end-stage renal disease (ESRD). Initial concern that removal of 50% of an individual's endowed nephron mass would commonly result in progressive renal failure has been assuaged by long-term studies of persons rendered 'uninephric' by trauma or surgery [1] and, more recently, by results seen in healthy kidney donors in single-center [2] and registry analyses [3]. These results collectively reassure us that short- and long-term risks of kidney donation are low, given our current screening practices. Recently, however, the issue of living donor safety has re-emerged because selection criteria for living donation have been liberalized, so that older persons and persons with hypertension, nephrolithiasis and glucose intolerance are now being considered as prospective kidney donors. These prospective donors are likely to have lower GFR than traditionally healthy donors, along with glomerulopenia [4–9].

Over the past decade, the US Division of Transplantation, the federal agency charged with administering contracts for organ allocation, has made living organ donation awareness a high priority to overcome the growing shortage of donors. This initiative has been so successful that in 2001 the number of live kidney donors exceeded that of deceased donors in the United States for the first time. The long waiting list for kidney transplantation, improved immunosuppressive protocols, the introduc-

tion of less invasive laparoscopic surgical techniques of donor nephrectomy, and increased awareness of the superior outcome of living donor transplantation have all contributed to increasing public awareness of the merits of living kidney donation. Potential living donors have volunteered in increasing numbers. As an unintended consequence, transplant centers are now faced with a substantial increase in the volume and complexity of living donor selection. Examples include the aforementioned expansion of the living donor pool, as well as novel approaches, such as paired-donor exchange, chain-donation and desensitization programs. These programs have drastically changed the demographics of live kidney donors from a primarily young, otherwise healthy group of first-degree relatives of recipients toward an increasingly older and often unrelated group of individuals, including some with disease processes of modest severity that were previously considered as standard criteria for exclusion. During the past two decades, the average age of living donors has increased steadily, such that the proportion of living donors >50 years of age has grown from 12 to 36%; the proportion of donors with pre-hypertension, hypertension and grade 1 obesity (body mass index 30–35) has also increased.

Coincidental with the increase in living donor utilization, clinicians have come to depend on clinical laboratories reporting an eGFR for a baseline assessment of kidney function. However, the original eGFR equation that utilizes serum creatinine concentration has evolved over the last decade. Such equations were originally derived in patients with chronic kidney disease (CKD), and most tend to underestimate GFR in persons with normal or near-normal kidney function. These equations were never designed for use in the healthy population, and results have often been misinterpreted to indicate CKD when none in fact exists. They are now being used by many transplant programs, both to gauge suitability for listing and for donor evaluation. Given the pressure of waiting times that now exceed life expectancy for the majority of the ESRD population, it is more important than ever to accurately determine the level of kidney function at which donor safety can be reasonably assured, while extending life in prospective recipients.

The convergence of these factors requires that we now re-examine our criteria for selection, and for follow-up, to ensure the safety and well-being of all living kidney donors. Indeed, the follow-up of living donors for at least 2 years is now recommended by UNOS, and efforts are being made to collect adequate information that is pertinent to their long-term well-being. Some would argue

that our traditional acceptance criteria for living donors are too stringent and conservative in the face of our current organ shortage. However, a major impediment to predicting the long-term safety of living donation is the requirement for follow-up that exceeds 20 years [1, 2]. As we move forward into uncharted territory, it is our responsibility to gain knowledge from this experience and more carefully screen and follow living donors who fall outside the safety margins of our time-tested tradition. We therefore recommend more accurate and rigorous testing of kidney function in donors who are compromised by advanced (>55) age, hypertension or glucose intolerance. Such donors are prone to glomerulopenia [8, 9], and hence may be at risk of developing progressive loss of kidney function following a halving of their nephron mass.

As stated previously, true GFR is the best measure of overall kidney function. We thus recommend that more, if not all, transplant centers, use the ‘gold standard’ filtration marker urinary clearance to ensure a level >80 ml/min/1.73 m² in the above-mentioned ‘at risk’ categories, so as to optimize the likelihood of identifying glomerulopenia [5]. We also recommend accurate imaging to determine renocortical volume, which reflects the number of filtering glomeruli [5]. We submit that attempts to develop a better eGFR formulation for this population will likely prove futile. In a recent report [10], we have shown that, because of the hyperbolic relationship between true GFR and serum creatinine, it is not feasible to develop a mathematical equation to accurately predict GFR from serum creatinine levels in the normal and near-normal range. For GFR in the 60–150 ml/min/1.73 m² range, the serum creatinine versus GFR profile is essentially flat and thus non-discriminating [10]. We are equally concerned about inappropriate application of such equations to uninephric individuals who have already donated a kidney, are otherwise healthy, and typically have compensatory hyperfiltration with true GFR in the 40–100 ml/min/1.73 m² range. Those with eGFR <60 ml/min/1.73 m² will frequently be mislabeled as having CKD by the MDRD definition, largely because of the systematic underestimation of true GFR. We re-emphasize that the range of serum creatinine levels in such donors is, typically only between 1.1 and 1.4 mg/dl, and is related only weakly to simultaneous GFR. In our opinion, it would be preferable to focus our efforts on making ‘gold standard’ measurements more accessible to this special population of patients, rather than to embark on a futile effort by pursuing a poor substitute. For those unable to establish a ‘gold standard’ GFR procedure, the best alternative

would be to approximate the GFR in those binephric potential donors with a marginal creatinine clearance (<90 ml/min/ 1.73 m²) after 3–4 days of cimetidine blockade of creatinine secretion.

The consequences of our changing selection practice will not be clearly apparent for many years. Hopefully, the implementation of new living donor registries will eventually quantify future risk to the expanded donor pool. A recent analysis of the UNOS donor registry regarding the change in donor procurement technique from a predominantly open nephrectomy to a laparoscopic one is reassuring. It indicates that the short-term risk of laparoscopic donation remains low [3]. Unfortunately, it also dem-

onstrates that the risk of mortality within the first year of donation is higher among donors with preexisting hypertension [3]. A modest additional risk may be acceptable to some donors, depending on their relationship with the intended recipient. Providing a higher level of care, oversight and follow-up in potential live kidney donors who are marginal either because of their age or of lower kidney reserve will provide not only an opportunity to learn more about the physiology of renal senescence in aging humans, but will ultimately identify safe criteria for living donors in the face of growing demand for solid organs. Now is the time to invest in accurate determination of kidney function in prospective donors!

References

- 1 Narkun-Burgess DM, Nolan CR, Norman JE, Page WF, Miller PL, Meyer TW: Forty-five year follow-up after uninephrectomy. *Kidney Int* 1993;43:1110–1115.
- 2 Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, Gross CR, Matas AJ: Long-term consequences of kidney donation. *N Engl J Med* 2009;360:459–469.
- 3 Segev DL, Muzaale AD, Caffo BS, Mehta SH, Singer AL, Taranto SE, McBride MA, Montgomery RA: Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010;303:959–966.
- 4 Tan JC, Workeneh B, Busque S, Blouch K, Derby G, Myers BD: Glomerular function, structure, and number in renal allografts from older deceased donors. *J Am Soc Nephrol* 2009;20:181–188.
- 5 Tan JC, Busque S, Workeneh B, Ho B, Derby G, Blouch KL, Sommer FG, Edwards B, Myers BD: Effects of aging on glomerular function and number in living kidney donors. *Kidney Int* 2010;78:686–692.
- 6 Keller G, Zimmer G, Mall G, Ritz E, Amann K: Nephron number in patients with primary hypertension. *N Engl J Med* 2003;348:101–108.
- 7 Nyengaard JR, Bendtsen TF: Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 1992;232:194–201.
- 8 Hoy WE, Bertram JF, Denton RD, Zimanyi M, Samuel T, Hughson MD: Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens* 2008;17:258–265.
- 9 Nyengaard JR, Bendtsen TF, Mogensen CE: Low birth weight – is it associated with few and small glomeruli in normal subjects and NIDDM patients? *Diabetologia* 1996;39:1634–1637.
- 10 Tan JC, Ho B, Busque S, Blouch K, Derby G, Efron B, Myers BD: Imprecision of creatinine-based GFR estimates in uninephric kidney donors. *Clin J Am Soc Nephrol* 2010;5:497–502.