Amending a historic paradigm for selecting living kidney donors

In this issue of the *American Journal of Transplantation* (AJT), Al Ammary and colleagues profile the decrease in living kidney donation in the United States from 2005 to 2017. Their optimistic comments notwithstanding, their data do not demonstrate specific changes in donor selection in response to new concepts of donor end-stage renal disease (ESRD) risk. The ongoing influence of classic teachings should not be underestimated. Centers may be more open to change if they know the history of the classic donor selection paradigm and how severely it has been compromised by new findings.

When the study began in 2005, the old paradigm held sway. The absence of certain predonation medical abnormalities was necessary and usually sufficient to allow donation. At 10 years postdonation, ESRD risk was no greater than the average risk in the general population, which seemed to validate this approach even for blacks, whose increased predonation risks were well recognized. The ethics were straightforward. If acceptable donation involved no increased risk, transplant centers “did no harm.” Nil risk was quantified and teachable risk. It applied equally to all candidates as an apparently fair and uniform threshold for donor acceptance.

When the old paradigm was ostensibly validated, our primary concern was postdonation hyperfiltration injury, which quickly caused ESRD in animal models. But over time attention has shifted to ESRD from specific postdonation kidney diseases. As an initially normal population ages, a variety of kidney diseases will begin and usually lose GFR slowly, resulting in a gradual, exponential accumulation of ESRD. In the general population, only 10% of lifetime ESRD occurs by age 44, and half occurs after age 64. This suggested that much of the 3.5% lifetime ESRD risk of unselected individuals would be unpredictable when they were young donor candidates. But the lifetime ESRD risk of middle-aged candidates who had remained free of kidney diseases would be much lower. From the standpoint of end-stage kidney diseases, older age in normal candidates was a new safety factor, as were high-normal predonation GFRs. These were unrecognized by the old paradigm.

Al Ammary does not find altered patterns of donor selection after 2014, when studies of postdonation kidney diseases from Johns Hopkins and other centers challenged the classic paradigm. Postdonation ESRD was indeed rare at 10 years, but increased exponentially, resembling ESRD in the general population. Well-controlled studies found an 8- to 11-fold increased rate of ESRD in donors vs matched nondonors. Such donation-associated risk was plausibly a result of lower postnephrectomy GFRs, causing new-onset postdonation kidney diseases to reach ESRD “ahead of schedule.” Although its exact magnitude was unclear, a risk of donation itself would amplify small differences in predonation risk. For example, a fourfold risk of donation changes a predonation ESRD risk of 0.5% to 2%, but a 1% predonation risk becomes 4%. Furthermore, low aggregate risks in postdonation cohorts concealed higher individual risks (for example, in certain biologically related donors and in blacks). In contrast to classic expectations, all donors appeared to take risk, and that risk could be quite variable. There was a danger of accepting donors at apparently high long-term risk and of refusing willing candidates at less risk than others whom we accepted. Determining individual risk was now difficult but still necessary. Specifically to address this daunting task, in 2017 the Kidney Disease Improving Global Outcomes consortium endorsed a creative algorithm to determine individual ESRD risk. But as with previous attempts, the algorithm’s low lifetime risk estimates for normal young candidates were implausible, and its methodology was problematic.

In 2018, new data from the University of Minnesota also contradicted the classic paradigm. Postdonation ESRD rates in whites increased from about 30/million per year in the first decade to about 2700/million per year at 30-40 years. By comparison, new-onset ESRD in the United States averages about 60/million per year from ages 20-30 years and about 950/million per year from ages 60-70 years. In other words, long-term ESRD rates in the putatively low-risk Minnesota donors appeared to be about 3 times those in the entirely unselected general population. This supported a need to supplement classic medical screening with age, race, and predonation GFR as additional epidemiologic tools to reduce long-term donor risk.

In summary, donor selection practices in US centers do not yet seem to have incorporated much of our new risk information. Yet, the risk of race and the safety of middle age can far outweigh risks of essential hypertension or a kidney stone. Lifetime ESRD is more likely with low normal predonation GFRs than with GFRs that are 50% higher. These epidemiologic risks of normal candidates are just as real as the predonation medical abnormalities of the old paradigm. We who have trusted the old paradigm should understand its limitations. Although major change occurs slowly and considerable uncertainty remains, we will hopefully soon use our best data to guide donor selection as we did in times past when we knew far less.

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