Is Hypertension Following Donor Nephrectomy Cause For Elevated Living Donor Kidney Function Concern?

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Beginning in the early 1990s, and despite improved public education and awareness of organ donation in the United States, the gap between the number of kidney donors and waiting recipients continues to grow. Although there are >100,000 patients listed for kidney transplantation, only one fifth are fortunate enough to receive the gift of life each year (1). This increasing organ donor shortage has resulted in a significant lengthening of pretransplant waiting times and has prompted many transplant centers to augment their efforts to promote living donor kidney transplantation.

Two large-scale studies, one from the United States (2) and the second from Norway (3), showed that the absolute risk of ESKD developing in living kidney donors was low, but significantly increased compared with matched nondonor controls (eight- and 11-fold higher, as reported in the American and Norwegian studies, respectively). This increased risk is significant, but the risk of a living kidney donor developing ESKD is well below the risk for the general population.

Although hyperfiltration-related injury may explain why donors in the American study progressed to ESKD, all nine donors who developed ESKD in the Norwegian study were biologically related to their recipient and shared with their recipients a predisposition for kidney disease (3). Similar factors might also explain an increased risk for hypertension development in kidney donors.

In this issue of CJASN, Holscher et al. (4) provide worrisome data that self-reported hypertension is nearly 20% higher in live kidney donors who were followed longitudinally for up to 27 years postdonation compared with relatively healthy, matched nondonors. This study confirms prior reports (5,6). Furthermore, their work goes on to show that the development of hypertension in former kidney donors is associated with an interruption in the slow rise in GFR that typically occurs over many years after kidney donation. It is important to emphasize that although subgroup analysis showed that black donors had a higher incidence of hypertension compared with white donors, the association between kidney donation and hypertension did not vary by race.

An ideally designed study to measure the risks incurred through kidney donation would require following a cohort of donors and perfectly matched nondonors. Recent studies (including that under discussion) have improved upon the former. But, as highlighted in expert commentary, the latter remains a challenge (7). Randomizing donor candidates to donation versus nondonation is both unethical and impractical. Therefore, studies attempting to ascertain the risks posed to former donors have derived their control groups from individuals enrolled in nontransplant-related research studies, particularly studies with sufficiently long-term follow-up during which kidney disease slowly develops. Holscher et al. crafted their control group using matched patients who participated in the Coronary Artery Risk Development in Young Adults (CARDIA) and Atherosclerosis Risk in Communities (ARIC) cardiovascular health studies (8,9). And, given that there are nearly 40% more kidney donors than healthy nondonor controls in the weighted study population, some matching with replacement was likely utilized.

Beyond the absence of a randomized control trial design, this study has several other limitations to which our attention should be drawn. The diagnosis of hypertension was on the basis of self-reporting by the former donors, not actual BP measurements. Therefore, for the purposes of this study, hypertension is a dichotomous variable. If, as suggested by Holscher et al., the development of hypertension in live donors leads to an interruption in the rise in postdonation GFR, a reasonable hypothesis would be that those donors with more poorly controlled hypertension would more likely be associated with the negative effect on filtration. Furthermore, the use of actual BP measurements would allow for confirmation that patients were correctly self-categorizing themselves as hypertensive.

The matching of the controls to the living donors in this study utilized propensity scores, a statistical technique that attempts to estimate the effect of a treatment (particularly one that cannot be easily or ethically randomized, such as living organ donation) by accounting for covariates that predict receiving the intervention. Although all measured covariates are balanced using this technique, there is always the possibility that unmeasured covariates affect the
quality of the matching. Indeed, we are only beginning to explore the hidden differences that make living kidney donors unique members of our society. In perhaps an extreme example of this, Marsh et al. (10), in their work to characterize extreme altruism, recently reported that being an altruistic kidney donor correlated with a larger right amygdala on magnetic resonance imaging.

The relationship between the donor and the recipient is another problematic potential confounder. Whether kidney donors who are blood relatives of their recipients are at a higher rate of progressing toward ESKD is unresolved (Muzaale et al. [2] showed an increased risk that did not reach statistical significance). Provided the same, or a similar, set of factors that account for this risk also confer a higher probability of developing postdonation hypertension, then a control group of individuals closely blood-related to a patient with ESKD is required to balance this potential confounder. A sufficient number of matching controls that have consanguinity with an individual affected by ESKD is unlikely to be found among the CARDIA and ARIC participants.

Holscher et al. report hazard ratios that were adjusted through propensity score weighting for age, race, sex, predonation eGFR, education level, and tobacco use history. They were not adjusted for baseline body mass index or predonation BP, which are both expected to affect the probability of developing hypertension.

In defense of Holscher et al., a methodological change in how BP are measured potentially lends additional support to the conclusions reached in their study. Both the CARDIA and ARIC cardiovascular health studies started in the mid-1980s. The Wellness and Health Outcomes in the Live Donor (WHOLE-Donor) study began assembling patients into the cohort earlier this decade. And, although some of the kidney donations occurred shortly after CARDIA and ARIC began collecting data, the participants Holscher et al. report on had a median follow-up of 6 years (interquartile range, 2–11 years; maximum 27 years). Therefore, the majority of the data collected on these kidney donors is from a more contemporary era than that of their matched controls. Although early oscillometric devices were available by the mid-1980s, both the CARDIA and ARIC study protocols prescribed the use of random zero (to reduce the risk of the operator bias in recording the final digit) mercury sphygmomanometers. More likely than not, the majority of patients in the WHOLE-Donor study had their BP measured using modern oscillometric devices. The significance of this instrument update being that oscillometric devices comparatively provide lower estimates of high BP (−1.6 mm Hg for systolic, and −0.6 mm Hg for diastolic) (9). This difference would be expected to bias the findings of Holscher et al. further away from the null hypothesis and further support the higher rate of hypertension development in kidney donors.

Disappointingly, the potential association between the use of antihypertensive agents in donors who developed hypertension and the interruption in the expected rise in GFR was not investigated in this report. Hence, it cannot be determined at this time whether the GFR trajectory change is directly triggered by a biologic mechanism attributable to hypertension or confounded by the use of particular classes of antihypertensive medications. To reduce the risk of hypertension induced microalbuminuria, treatment with angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs) is recommended in kidney donors (6). Further, treatment with ACEI and ARBs can clearly interfere with the autoregulation of GFR. Despite this, the use of ACEI and ARBs was separately shown to be associated with both a lower risk of eGFR <45 ml/min per 1.73 m² and less ESKD in a predominantly white cohort (5).

Although there was initial concern that the studies reporting an increased risk of ESKD in live donors might have a meaningfully negative effect on the rate of living donation in the United States, the number of living donors per year has increased since their publication. However, the educational presentations and informed consent conversations between transplant professionals and donor candidates shifted from one that suggested there was no “proven” risk to donors to one that is enlightened by improved quantification and growing evidence from larger cohorts.

If corroborated, the findings presented by Holscher et al. are anticipated to have a meaningful effect on the transplant community across multiple dimensions, including the informed consent process, and policy decisions regarding obligations for the parent center to provide truly long-term (decades) follow-up for their living donors. These findings also have the potential to further shift the public and media’s perception of the safety of living kidney donation, especially when coupled with the earlier reports already indicating an increased risk of ESKD in living donors. Hopefully, the WHOLE-Donor study cohort will continue to grow and be followed into the distant future and provide added insights pertaining to the effects of postdonation hypertension development. Whether this subgroup of donors that develops hypertension goes on to develop kidney and cardiovascular disease at a higher rate will be of particular interest.

Disclosures

Dr. Asch has nothing to disclose.

References
