EDITORIAL

Donation-Attributable Risk—A Call to Action

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"Practice two things in your dealings with disease: either help or do not harm the patient."[1]
***Primum non nocere*—Hippocrates (460-370 BC)**

The Hippocratic Oath is foundational to how we practice medicine emphasizing the ethical principles of beneficence and nonmaleficence; yet in 1954 we challenged these notions when for the first time in human history we performed surgery to remove a kidney from a living person for the purpose of transplant—a surgery that offered no medical benefit to the donor, the patient.[2] We have balanced the ethical dilemma living donation poses by embracing a standard of care that mandates "the benefits to both donor and recipient must outweigh the risks associated with the donation and transplantation of the living organ donor."[3,4] Benefits and risks, foundational knowledge required for informed consent or autonomy in decision-making. In other words, to justify violations of the ethical principles of beneficence and nonmaleficence, our current standard mandates that at minimum we understand donation-attributable risks. Balancing risk requires us to effectively communicate risk to donors, the patients, but importantly requires us to understand what those risks are. Donation-attributable risk is a concept that has proven challenging in our field as it requires us to isolate the added risk kidney donation itself may play in comorbid disease development across a donor's life span.[5] Studies have been hampered by the lack of actual nondonor controls—individuals meeting living kidney donor criteria, evaluated and approved for living donation, but ultimately never donated, creating knowledge gaps in our understanding of donation-attributable risk and our ability to provide informed consent.[5]

The needle on our understanding of donation-attributable risk for hypertension has definitively moved as Garg and colleagues[6] report results from their prospective cohort study that included the most rigorous and robust cohort of nondonor controls ever reported for assessing donation-attributable risk that achieved the highest score for methodological quality on the Newcastle-Ottawa Quality Assessment Scale. Nondonor control participants included individuals who were evaluated and approved for living donation but did not go on to donate and who underwent follow-up measurements and testing with the same frequency and intervals as the living donors. Over a median of 7 years of follow-up with more than 100 000 blood pressure measurements, the authors found no difference in hypertension or albuminuria between donors and nondonor control participants, and as expected with aging, donors and nondonors had a similar average increase in systolic blood pressure. Moreover, they demonstrated that at 12 months postdonation, donors had a slower rate of decline in estimated glomerular filtration rate (eGFR) compared to nondonors.[6] These results are encouraging and provide real-world evidence that uninephrectomy does not increase a living donor's future risk for hypertension. Knowledge gap addressed; autonomy in decision-making enhanced.

The gap addressed, however, is much smaller than we hoped. While impressive in duration, follow-up, and robustness of nondonor controls, the Garg et al study is hampered by an ethnically and racially homogenous donor population, with only 14 of 954 donors identifying as Black, that no longer reflects modern-day living kidney donor populations as the study cohort had a median BMI (calculated as weight in kilograms divided by height in meters squared) of 26 and 25 among donors and nondonor controls, respectively.[6] This lack of generalizability is poignant as hypertension has been recognized as a precursor and cause of future kidney failure.[7] We know, for example, kidney risk genetic variants, such as apolipoprotein L1, which are unique to individuals with African ancestry, are associated with a 7-fold increased risk of hypertension-related kidney failure,[8] and that obesity (BMI ≥30) accounts for 25% of the US kidney disease burden both directly through hyperfiltration and indirectly via obesity-related conditions like hypertension.[9-11] Importantly, studies have shown that race and the presence of obesity independently predict eGFR recovery in living kidney donors, such that Black individuals were 1.9 times less likely to recover 60% of their predonation eGFR and time to recovery was 1.1-fold slower in obese donors,[12] and may explain the increased postdonation kidney failure risk observed in Black[13] and obese[14] donor populations. Moreover, obese living donors who experienced more than 5% postdonation weight gain were observed to have a 2-fold greater incidence of postdonation hypertension and among Black obese living donors the incidence was 3-fold higher.[15] Lower eGFR in the early postdonation period and hypertension have been independently associated with increased risk for future kidney disease development.[16] These statistics are staggering and highlight the need to understand donation-attributable risks, particularly those risks that are modifiable like obesity, that reflect current living donor populations to ensure living donor safety and autonomy in decision-making.

If we are to mitigate the impact of the conscious decision to set aside the ethical principles of beneficence and nonmaleficence that living donation requires, we must continue to aggressively address knowledge gaps in our understanding of donation-attributable risks as we are obligated to uphold and reinforce the underpinning of informed consent with the ethical principle of autonomy in decision-making. True autonomy in decision-making requires knowledge. Without question, Garg and colleagues have set the bar for identifying

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appropriate nondonor controls who are crucial for assessing donation-attributable risks, but knowledge gaps remain. The lack of generalizability to modern-day living kidney donor populations is a call to action for enhanced prospective living donor and living donor candidate follow-up. We have sworn an oath to our donors, our patients: primum non nocere.

ARTICLE INFORMATION

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