Special Section: Open Forum

The Risk in Living Kidney Donation

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Abstract: This article examines two questions. (1) If prospective living kidney donors knew of the lifetime risk of end-stage renal disease (ESRD) in their remaining kidney, then would they be as willing to give it up? and (2) What should transplant organizations and physicians be telling those who express an interest in donating a kidney about risk? Based on the principle that prospective donors must be fully informed of the risk, I raise the issue of a possible obstacle to closing the gap between the availability and need of transplantable kidneys. Some strategies are offered to address this problem.

Keywords: kidney transplant; living kidney donors; end-stage renal disease (ESRD); donor risk

Introduction

In a recent survey conducted by a group of researchers on living kidney donation, 68 percent of slightly more than 1,000 respondents said that they would be willing to donate a kidney to anyone in urgent need of the organ, and 23 percent said that they would donate to select recipients. Only 9 percent said that they would be unwilling to donate. Approximately 60 percent said that monetary compensation of $50,000 would make them even more likely to donate, although 32 percent indicated that monetary incentives would not affect their desire to donate.[1] The high percentage of responses in favor of donation seems a positive sign in light of the gap between the number of kidneys available for transplantation and the number of people who need them. The ability of transplant programs to facilitate the translation of wishes to donate into actual donation would go some way toward closing this gap. It is not clear what reasons were behind the responses of those who said that they would not donate. However, all of the responses prompt the following questions. If prospective donors knew of a long-term risk of disease in their remaining kidney, then would they be so willing to give one up? What should transplant organizations and physicians be telling those who express an interest in donating a kidney about the risk?

Risk Assessments

Two factors could largely explain a general minimal consideration of risk by prospective donors. One is the association of risk primarily if not exclusively with the nephrectomy itself. The risk of perioperative and postoperative complications from unilateral laparoscopic nephrectomy is 10–15 percent.[2] These include, but are not limited to, bleeding, infection, bowel injury, hernia, and post-anesthesia depression. The responses from those interviewed in the survey suggest that many believe that this is the extent or the main source of risk. Although they may know

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that some kidneys from living donors fail in the recipient shortly after transplantation, they may not give much thought to any conditions that could develop in the donor long after nephrectomy. A second factor is the belief that we only need one kidney and, therefore, could live just as well with one as with two. Many assume that this is a redundancy not necessary for adequate filtration of waste products and other metabolic functions, as measured by the glomerular filtration rate (GFR), which is the most accurate measure of kidney function. But this belief fails to appreciate the fact that there is a loss of renal reserve in an approximate 30 percent reduction of GFR after nephrectomy.[3] It suggests that there may be a good reason for the presumed redundancy in having two kidneys in sustaining renal function in the face of medical conditions that can adversely affect this function as we age. Nevertheless, some retrospective studies following kidney donors for up to 15 years post-donation seem reassuring about risk. They indicate that the incidence of end-stage renal disease (ESRD) in donors deemed healthy at the time of donation is approximately 3 per 1,000 at 15 years.[4] This compares favorably with matched healthy non-donors over the same period. Even with an immediate reduction of GFR from nephrectomy at donation, the studies suggest that the risk of developing ESRD from living kidney donation is not significantly higher than the risk for the general population.

However, transplant organizations have misleadingly modelled post-donation ESRD as rare. ESRD takes decades to evolve. There is a "honeymoon" period immediately after donation, because healthy donors by definition start out with normal kidney function. Kidney disease typically takes 20–30 years to develop in the general population. It may take even longer to develop in healthy donors.

More recent analysis of the data suggests that the standard 15-year period of monitoring function of the remaining kidney is not long enough and does not provide an accurate measure of risk. Monitoring kidney function over the remaining lifetime of the donor is necessary to capture the real risk. One-third of living kidney donors in the United Network for Organ Sharing (UNOS) registry are under age 35. The analysis suggests that, for a healthy 25-year-old with no detectable medical conditions at donation, there may be an 8–11-fold increased relative risk of developing ESRD from donating by the time he or she reaches 80 years of age.[5] According to the most recent data, even the 15-year post-donation ESRD risk is higher than the estimation in the studies mentioned earlier. The risk for this period among living kidney donors in the United States was 3.5–5.3 times as high as the projected risk in the absence of donation.[6]

Lifetime risk can be attributed to the combination of reduced GFR and the development of diseases such as type 2 diabetes, hypertension, and glomerulonephritis, which impair kidney function and typically affect people later in life. More precisely, the *relative* risk is all caused by the loss of GFR. The *absolute* risk is caused by the probability of diabetes and other kidney diseases. These diseases would not be present when a 25-year-old consented and was allowed to donate. If they had been present, then they would be excluding conditions. Data on the incidence of subsequent ESRD in donors in the 15-year evaluation models do not adequately account for factors that could compromise kidney function as the donor ages.[7] With the exception of known inherent risks of kidney failure from conditions such as polycystic kidney disease, as well as a higher incidence of genetically and environmentally influenced hypertension and diabetes among blacks, the risk of developing chronic conditions that could compromise long-term kidney function

may not be known or may be ambiguous when a younger individual donates. Older individuals in the 50–60 year range may be excluded from donation if they already have or show early signs of diabetes or hypertension, because of the effects of these conditions on kidney graft survival in transplant recipients. However, younger individuals with no signs of kidney-affecting diseases may be exposed to long-term risk by donating and reducing their GFR. This may be unfair to the younger cohort if, unlike their older counterparts excluded from donation, they are exposed to a greater risk of ESRD later in life based on being healthier and more appropriate candidates at the time of donation. One way of emphasizing the consequences of reduced GFR is that what would have been fairly common mild kidney disease in the lifetime of a person with two kidneys may become ESRD in the lifetime of a person with one kidney.

Presumably, the benefit of living kidney donation outweighs any harm. The transplant recipient benefits physiologically from receiving a healthy kidney and psychologically from survival and improved quality of life in not having to continue undergoing dialysis. The donor benefits psychologically from knowing that his or her action saves and improves the quality of the recipient's life. However, if a donor develops ESRD as a consequence of combined reduced GFR and chronic kidney-affecting diseases later in life, then the overall combined benefit to recipient and donor may be less than what many believe. This requires reconsideration of the weighing of benefit and harm of living kidney donation. It requires a change from a shorter-term to a longer-term risk framework to assess the overall value of this action.

Risk and the Duty to Inform

The data on the lifetime risk of ESRD for living kidney donors generate an ethical obligation for transplant nephrologists and surgeons to fully inform prospective donors of this risk. This obligation is grounded in the bioethical principles of respect for patient autonomy and nonmaleficence.[8] Like any patient undergoing a surgical procedure or other intervention in the body, prospective kidney donors have the right to be fully informed of the immediate and long-term risk in order to make a deliberative, rational decision about donation. Medical practitioners have a duty to provide data about this risk to those who are healthy when they express an interest in giving up a kidney for transplant. In addition, medical practitioners have a duty not to expose patients to undue risk of harm. They key issue is baseline risk. If the baseline risk is 0.01 percent, then an eightfold increase is not so important. But a young person with a low GFR has a pre-donation baseline risk of approximately 5 percent. This is higher among blacks. If this is multiplied by a factor of five corresponding to the number of years after donation, then there is a very tangible risk. It is debatable whether an 8–11-fold increased relative risk of ESRD in donors over a lifetime can be considered *undue* risk, especially when such an outcome is not certain and is influenced by genetic, environmental, and other factors. However, it should be a factor in weighing the benefits and burdens of this type of organ donation.

Some and, perhaps, many donors would still donate knowing the real risk. But this would not diminish the physicians' obligation to inform them of not just the 15-year but also of the lifetime risk of ESRD. Failure to do this would be a violation of respect for patient autonomy and could also violate the duty of nonmaleficence.

This could occur if donors acted on the belief that the risk was lower than what the data indicated, and they developed renal complications 20 or 30 years after donation. Transplant nephrologist Robert Steiner is more specific in explaining what discharging the duties of respect for autonomy and nonmaleficence entails for the selection of living kidney donors: "We cannot tell some candidates that their lifetime risks are 'minimal' when we have good reason to believe that they could easily be 10% or greater. We also cannot say that we have 'no idea' of risk when in fact we know a great deal about risk. And we would not be protecting the donor if we allowed donation with no idea of risk."[9] Informed consent to living kidney donation requires knowledge that the initially low ESRD risk among young adult donors increases exponentially over time.

Medical nonmaleficence is not an absolute obligation, because drugs and surgical procedures needed to treat diseases may have harmful side effects. Physicians may have a secondary duty to promote organ donation and transplantation as one way of promoting public health. However, this secondary duty should not supersede physicians' primary duty to prevent harm to their patients. Harm prevention includes the act of fully informing patients of any and all risks of an intervention in the body, and harm includes not just adverse events occurring shortly after a procedure but over the course of the patient's life. As an expression of their autonomy, competent patients have the right to expose themselves to a reasonable degree of risk. Yet even if there is disagreement about what constitutes *reasonable* or *undue* risk, physicians have an absolute obligation to inform people expressing an interest in living kidney donation of the known lifetime risk from donating.[10] If physicians are unsure about this risk based on the available data, then the default position should be to discourage people from donating.

Prospective donors, fully informed of the lifetime risk, may discount it and decide to donate in any case. Provided that their reasons for donating were acceptable to the transplant team, a decision to donate that discounted but did not ignore the chances of kidney failure in the future could be considered an autonomous, rational decision. In such a case, a paternalistic argument against allowing these individuals to donate in order to prevent harm would not be defensible. Temporal discounting by itself is not evidence of irrationality or ignorance of risk. Some might claim that offering $50,000 to donate would be an undue monetary incentive that would cause a donor to pay less attention to or ignore data about risk. But such an incentive would not necessarily compromise the individual's rational decision-making. Here, too, paternalistic reasons for not allowing donation because of these incentives could be overridden by respect for the autonomy of the prospective donor in deciding to donate.

Still, the consequences of risk realized in actual ESRD would not be limited to the patient alone. A donor whose remaining kidney fails to function years after unilateral nephrectomy will contribute to healthcare costs associated with dialysis and kidney transplantation. These costs would not have resulted if the young donor had not given up his or her kidney. Some degree of paternalism might in principle be justified if the outcome were preventable and would add to healthcare costs. One way around paternalism would be to adopt the libertarian view that potential donors aware of the risk be allowed to donate on the condition that they would pay the total cost of dialysis or kidney transplantation if they developed renal failure as a result of their donation. This does not mean that living kidney donation should be much more restricted, but it underscores the need for

more careful screening of prospective donors to identify what could be indicators of future functional failure in the remaining kidney. These would include low-normal GFR for healthy individuals of 40 years or younger and those with high-normal blood glucose or blood pressure levels. However, even better screening will not absolutely predict which donors will actually develop ESRD. This may not be known at the time of donation and underscores the need for data indicative of long-term risk. If we could predict that a 25-year-old donor would develop ESRD 20 years after donation, then this would be 10 percent of his or her lifetime risk. Half of lifetime ESRD occurs after age 63. An increase in the incidence of donation-related ESRD would not exacerbate the current organ shortage or substantially increase healthcare costs, because healthy kidneys would be transplanted and transplant recipients would no longer need dialysis. Yet the fact that some donors will develop ESRD suggests that living kidney donation might not alleviate the chronic shortage of transplantable kidneys and reduce costs associated with dialysis as much as many might be inclined to believe. Delayed harm to at least some donors and some increase in healthcare costs could be consequences of immediate benefit to recipients.

The lifetime relative risk of kidney disease among donors compared with non-donors could have important implications for regulated organ markets and paired living-donor kidney exchanges. Although unregulated sales of organs have been conducted for some time, a regulated market is still hypothetical.[11] Paired exchanges have been one way of enabling transplantation by overcoming immune incompatibility.[12] Both models rest on an assumption of minimal risk in donating a kidney, and this is typical in most promotions of living donation. It is unclear how much of an increase in the relative risk of kidney failure for young donors would be considered reasonable and justify donation within either system, but it could influence the incentive to donate. Many donors in paired exchange programs overlook risk in order to save a loved one. Nevertheless, it is possible that more risk-averse prospective donors who conditionally agreed to donate in a paired exchange might have second thoughts and be reluctant to donate in light of their knowledge of a 10 percent lifetime risk (of ESRD). If they changed their minds and decided not to donate, then this could disrupt the transplant chain and preclude some potential recipients from receiving a transplant. It could have significant adverse effects if the exchange involved many potential donors and recipients. This highlights the problem of estimating real risk, and raises questions about the medical and ethical justification for unreservedly allowing healthy young people to donate.

Alternative Strategies

Recent findings about desensitization of the immune response may allow transplants between immunologically incompatible donors and recipients.[13] This process would reduce the probability of rejection, improve graft survival and increase the number of successful kidney transplants. However, whereas immune desensitization would improve outcomes for transplant recipients, it would not reduce the lifetime risk of ESRD for young donors.

If the largest source of kidneys from living donors were reduced because the lifetime risk of unilateral nephrectomy was deemed unacceptably high for younger donors, then this would be an obstacle to closing the gap between the availability

and need of transplantable kidneys. One way of partly resolving this problem would be to continue allowing donation from older individuals 50–60 years of age with conditions excluding them from donating under current criteria. This could even be extended to individuals 60–70 years of age. Steiner proposes two strategies to equalize lifetime risk among prospective donors of different cohorts and ethnic groups so that some are not exposed to greater risk than others: "To achieve a defensible, uniform risk standard, we have only two choices: to minimize risk by accepting only completely normal, nonblack older donors with high-normal GFRs, or to endorse a somewhat liberalized risk threshold which would mean declining many acceptable young black, and /or low GFR donors and accepting many more older candidates with medical abnormalities."[14] These would be abnormalities that would have little effect on long-term renal risk. Such abnormalities might entail a shorter life expectancy; but a shorter life would not be caused by renal failure. It is open to debate which of these strategies would do more to protect potential donors without reducing the donation rate.

Conclusion

The most obvious and effective strategy would be to prevent or substantially reduce the incidence of ESRD in the general population. This would require the ability to control the processes through which genetic, physiological, and environmental factors contribute to kidney failure. Unfortunately, this control has not yet been achieved. Regenerative medicine that repaired or replaced failed kidneys would be highly desirable, although this research is still at a very early stage. As long as living kidney donation is necessary to partly meet the need for solid-organ transplantation resulting from kidney failure, healthy donors may be putting themselves at a significant risk of developing ESRD later in life. Transplant nephrologists, surgeons, and indeed all healthcare professionals have a duty to acknowledge what the effects of unilateral nephrectomy on GFR in the remaining kidney imply for the lifetime risk of ESRD. They must fully inform prospective kidney donors—younger and older—of this risk of donation in discharging their duty to respect their autonomy and protect them from preventable harm.

Notes

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