What happens to the live donor in the years following donation?

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Kidney donors are healthy people undergoing nephrectomy for the benefit of another individual. This is a special situation in medicine and requires discussion of potential risks related to donor nephrectomy.

Up to the year 2000, there were several reassuring reports regarding the long-term risks of living donation [1, 2]. A Swedish study even showed that living donors lived longer than the general population [3]. Recently, however, observation of much larger cohorts (>1000 living donors), coupled with prolonged follow-up and the use as controls of people free of comorbidities instead of the general population, has allowed better assessment of the incidence of rare events such as end-stage renal disease (ESRD) and death among former kidney donors [4, 5].

Regarding ESRD, there is no reason to believe that having only one kidney increases the risk of getting kidney disease. However, if a donor develops kidney disease, starting out with one kidney instead of two is likely to increase the risk of needing renal replacement therapy [6]. Two articles published in 2014 found a 7–10 times increased relative risk of ESRD in previous donors. First, a US study of 96 217 kidney donors, with a median follow-up of 7.6 years, found that the risk of ESRD 15 years after donation was 0.31% in kidney donors and 0.04% in their matched healthy non-donor counterparts [5]. The absolute risk of ESRD was 3-fold higher in blacks than in whites, and higher in men than in women. Of note, the risk of ESRD was around 20-fold higher in unscreened non-donors (general population) than in the healthy cohort, explaining some of the previous favourable findings. Second, a study from Norway included 1901 donors followed for up to 48 years [4]. Similar to the US study, the rate of ESRD at 15 years was 0.46% in donors and 0.06% in the selected control healthy population. ESRD was a late event, occurring at a median of 18 years after donation. A recent study by Matas et al. [7] also found that ESRD developed at a mean of 27 years after donation and was almost always due to a new-onset disease [7]. Of importance to clarify for potential donors and recipients, even if the relative risk of ESRD is quite large (5–10 times) after donation, this translates into a very low increase in absolute risk (<0.5% at 15 years) if the baseline risk is low, for example, in a healthy white 50-year-old donor. An example of the difference between relative and absolute risks is that even if you buy 10 lottery tickets instead of 1, your chance of winning the lottery is still be quite small, even though it becomes 10 times greater. Finally, there are two important notions to consider: first, the lifetime risk of ESRD in former donors is higher in young than in older donors. Indeed, the two most frequent causes of ESRD in former donors are diabetes and hypertension [7], which both develop mainly after the fourth decade. Thus a normal workup in young donors is unlikely to identify those who will later develop diabetes or hypertension, while these diseases would disqualify older donor candidates in case they occurred [8–10]. Second, the baseline risk of ESRD could be higher in first-degree relatives than in unrelated donors. This reflects the well-known genetic component underlying the development of ESRD [11]. As an aid to clinicians, a number of freely available calculators allow the estimation of each individual donor’s risk of ESRD after donation [12–14]. However, these calculators are not yet well validated and have been criticized for being created from cohorts with short follow-up times, thus underestimating long-term risks of ESRD due to risk factors developing after many years of observation, for example, diabetes [15]. Particular care is needed when assessing the most high-risk donor candidates: young, black and first-degree relative to the recipient. We present in Figure 1 an algorithm to help evaluate the suitability of kidney donation according to the risk of later ESRD.

The next crucial question is whether living kidney donation increases mortality. Several studies have shown that kidney donation might worsen, although minimally, some cardiovascular risk factors. A meta-analysis concluded that kidney donors may have a 5-mmHg increase in blood pressure within 5–10 years after donation over that anticipated with normal ageing [16]. In controlled studies, urinary protein was higher by ~70 mg/day in donors than in controls [17]. One multicentre study of living kidney donors and healthy controls (n = 124) revealed a small but significant increase in left ventricular mass at 12 months [18]. Finally, there is a known increase in cardiovascular events and mortality when glomerular filtration rate decreases to substantially <60 mL/min [19].

What about the risk of death among former living donors? A recent meta-analysis suggested no evidence of a higher risk for all-cause mortality or cardiovascular disease among former donors [20]. There was, however, heterogeneity among the
three studies reporting these outcomes [21]. Two large and well-designed studies from the USA and Canada did not find any difference between donors and controls, but the median follow-up time was short, ~6 years [22, 23]. In contrast, a Norwegian study with long-term follow-up found significantly increased risks for both all-cause mortality and cardiovascular mortality compared with healthy controls [4]. The median follow-up was 15 years (range 1–48) and the difference between donors and controls was revealed only after >10 years of follow-up time, indicating that a long period of observation is necessary to uncover this relationship. After 25 years, the absolute risk for all-cause mortality was 5% higher in former donors. Accordingly, one could say that there is no increased mortality during the first decade after donation, but one study found increased mortality after more than a decade of follow-up. There are, however, some biases in these studies. In all three studies, the majority of donors were related to the recipient, making it difficult to separate consequences of nephrectomy from genetic factors. As previously argued [24], this ‘plus 5% mortality’ might be an overestimation due to the confounding effect related to a family history of renal disease. Indeed, not only the baseline risk of ESRD is increased in patients having a first-degree relative with ESRD, but also the baseline risk of death [25]. Finally, donors and controls in the studies from the USA and Norway were drawn from different geographical areas. Thus the increased risk of death, if present, occurs late after donation and is likely to be limited. Further studies are needed to better evaluate this risk.

In summary, what happens to the live donor in the years following donation? A high relative but small absolute increase in the risk of late ESRD and a possible (to be confirmed) increased risk of death more than one decade after living donation. Acknowledgement by the transplant community that living kidney donation is associated with long-term risks is likely to have consequences for the evaluation and selection of future donors. Since these risks seem to be evident only after long-term follow-up, remaining lifespan after nephrectomy becomes in itself a risk factor. Consequently we would recommend increased interest in older donors since these may actually be those facing the lowest risks after donation [10]. Transplant centres should try to present the donor with rough risk estimates based on recent literature. The transplant team should also inform the donor that a healthy lifestyle post-donation together with lifetime outpatient clinic follow-up are definitely needed to maximize donor health in the long-term.

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CONFLICT OF INTEREST STATEMENT

None declared.

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