Why did mother nature provide us with two kidneys?

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Kidney transplantation is the treatment of choice for patients with end-stage renal disease and since many years transplantation from living donors is considered to be the optimal choice with the best outcome for the recipients [1,2]. Due to this fact and the lack of cadaveric donors, it is not astonishing that a certain pressure arose to recruit living donors [3]. Reports that living donation is safe are therefore important and would justify this treatment of choice for our recipients. But is kidney donation really safe [4]. Reports that living donation is safe are therefore important and would justify this treatment of choice for our recipients. But is kidney donation really safe?  

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for the donor? If it is possible to remove one kidney without long-term harm, why did mother nature give us two? Therefore, the question has to be asked: do the current studies, analyzing the outcome of living donors, correspond to the highest standards in order to draw sound conclusions?

One of the first facts we learn in renal physiology is that removing one kidney results in hyperperfusion and hyperfiltration and this in turn leads to damage of the remaining kidney with albuminuria and decreased renal function. Is this also true for healthy living kidney donors?

A study prospectively measured renal function by inulin and Para aminohippurate clearance, albumin excretion and blood pressure before uninephrectomy and 1 week and 1 year after donation [4]. The authors found that hyperfiltration averaged 128% and hyperperfusion 133% 1 week after uninephrectomy. One year after donation, hyperfiltration was nearly unchanged (126%), whereas hyperperfusion significantly decreased to 118%. Albuminuria was found in two donors 1 week and in two donors 1 year after donation. This carefully done study clearly shows that the first part we learned in renal physiology, i.e. uninephrectomy results in hyperperfusion and hyperfiltration followed by albuminuria is also true in kidney donors. Does this also result in a decline of renal function?

In this issue of *Nephrology, Dialysis, Transplantation*, Fehrmam–Ekholm et al. [5] tried to answer this question with an analysis of ‘post nephrectomy development of renal function in living kidney donors’. Interestingly and against the theory, they found that renal function of the remaining kidney improves for many years in living donors. Mean estimated glomerular filtration rate (eGFR) of the investigated donors increased for 15–17 years after donation, remained constant for 8 years and only 23–25 years after donation the expected decline in renal function could be detected. Although others could show that the remaining kidney function improves after donation [6,7], the new finding of Fehrmam–Ekholm’s study is the very long adaptive process, which is somewhat surprising. The strength of the study is the large number of living kidney donors, the long-time period after donation and the homogenous and strict criteria of donor selection, which did not change during the study period. The disadvantage is the cross-sectional study design. From the original cohort of 1110 living donors, only 573 donors were analyzed. Although the follow-up went up to 43 years, the mean time since donation was ‘only’ 15 years. Important for the finding of this study is the methodology, as the main result is not a direct observation but a calculation. However, the regression functions take into account both age at the time of the follow-up examination and time since donation as independent variables and therefore should be sound.

What does the literature teach us about renal function after living donation? A variety of studies were published, which tried to analyze renal function after donation and the long-term risk for kidney donors [8,9]. Probably, the largest single center investigated cohort consisted of 3698 kidney donors, who donated between 1963 and 2007 [10]. Interestingly, they also found that a longer time since donation was associated with a higher glomerular filtration rate (GFR) and that renal function remained stable in donors with two serial GFR measurements. However, of the 3698 kidney donors, only 255 had GFR measurement and the course of renal function was analyzed in only 38 donors! Similar results were shown in a meta-analysis which summarized a total of 5048 donors in 48 studies from 27 countries [11]. Seven years after donation (range 1–25 years), the average GFR was 86 mL/min. The authors reported that 12% of the donors developed a GFR between 30 and 59 mL/min and 0.2% a GFR <30 mL/min [11]. Taking these results together, renal function seems to initially fall after donation by ~25–30% but remains stable or even increases thereafter.

How about proteinuria? The study of Fehrmam–Ekholm et al. [5] reports that one in five donors demonstrated albuminuria. A finding which was confirmed by most of the studies [11–15]. Urinary protein was usually reported to be higher in donors compared to controls and became more pronounced over time.

Going back to our physiological understanding, it is clear that donors do demonstrate hyperfiltration and, most likely as a consequence, have albuminuria after uninephrectomy. However, on the contrary to what we would expect, kidney function seems to be stable for many years. Nevertheless, long-term studies also reveal that some of the donors have a renal function <60 mL/min [11] and the question arises if this has an impact on secondary complications. This indeed seems the case, as 20% of the donor population in the study presented in this issue has an elevated parathyroid hormone [5]. Does impaired renal function with the proven secondary complication have a negative impact on the survival of donors? This does not seem the case, as several studies demonstrate similar survival of donors compared to control groups [8,14].

In summary, we can say that living kidney donation is a safe procedure, if we consider the published literature as representative. But is this the case? Most studies have been conducted at single centers with selected, primarily white individuals. Can we generalize from this restrictive sample? Most likely not! Storsley et al. [15] report that 42% of aboriginal donors have hypertension compared to only 19% of white donors in their follow-up. Moreover, all aboriginal donors in this analysis developed hypertension 20 years post donation.

Control groups are often confounded reference populations and the question has to be asked: what is the appropriate control to compare outcome in living donors? The best control would be accepted donors who cannot donate due to a problem of the recipient. However, these nondonors are very difficult to recruit and to follow. It is therefore not astonishing that most studies use ‘inappropriate’ controls. As an example, one study shows better survival of kidney donors when compared to the normal population [16]. This result is the consequence of a positive selection bias and demonstrates the necessity of appropriate controls.

The next point to mention is that the event rate—in particular survival or end-stage renal disease—in living donors is very low. Therefore, the power to detect statistical differences is rarely reached. Moreover, most of the studies are retrospective analyses, with all the problems of such approach. There is only one nationwide registry, which follows the donors prospectively since >18 years [7]. Renal function of donors reported from this registry falls after
Donor selection criteria also have an impact on long-term outcome. Sweden has very strict donor criteria, as no hypertensive donors are accepted, which is not the case in other countries. It seems obvious that donors with e.g. hypertension at the time of donation will more likely have impaired renal function over time. This is probably not a problem for donors aged >60 years, but most likely for younger donors.

From these considerations, we can conclude that published studies in regard to long-term follow-up of living kidney donors have some limitations. Thus, we are in need of prospective long-term data not only to improve our knowledge but also to detect donors with a decrease in renal function in order to intervene and prevent these donors from reaching end-stage renal disease. Therefore, I do not share the opinion of the authors, who report in this issue of Nephrology, Dialysis, Transplantation, that regular medical follow-up examinations are superfluous!

In conclusion, why did mother nature provide us with two kidneys? Renal function is crucial and therefore nature supplied us with a reserve in case of kidney disease or if we damage one kidney. Fortunately, most of us do not need this reserve. It seems that nature gave us too much kidney mass for one lifetime—at least to the selected donors reported in the literature!

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