Post-nephrectomy development of renal function in living kidney donors: a cross-sectional retrospective study

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Abstract

Background. Increasing numbers of living donor kidney transplantations calls for better knowledge about long-term donor outcomes and risks.

Methods. To explore long-term kidney donor outcomes and risks, we conducted a cross sectional retrospective study. To this end, we analysed renal function using measured glomerular filtration rate (mGFR) and estimated glomerular filtration rate (eGFR) as well as microalbuminuria, blood pressure (BP), body mass index, haemoglobin, albumin and parathyroid hormone in kidney donors nephrectomized between 1965 and 2005.

Results. A total number of 573 kidney donors agreed to undergo medical follow-up examinations. The mean age (standard deviation) at donation was 47 (11) years and the mean time since donation was 14 (9) years. Both mean mGFR [68 (15) mL/min/1.73m² body surface; P = 0.028] and mean eGFR [71 (16) mL/min/1.73m² body surface; P < 0.001], based on modified diet renal dysfunction and iohexol or Cr-EDTA clearance, respectively, were found to decrease with age and to increase with time since donation. Special multivariable regression analyses reveal that for 30-year old donors, the median eGFR typically increases during the first 17 years, then remains constant for ~8 years and slowly declines thereafter. For 50-year-old donors, the median eGFR is expected to increase during the first 15 years or so and then to enter a phase of slight progressive decline. In total, 23% (126/546) of the donors were on antihypertensive medication. An additional 22% (117/543) of the donors were found to suffer from hitherto undiagnosed hypertension (BP >140/90 mm Hg).

Conclusion. Renal function of the remaining kidney in living donors is expected to improve for many years but will show signs of slight deterioration in the longer run.

Keywords: eGFR; hypertension; kidney donation; mGFR; microalbuminuria

Introduction

With more living kidney donors worldwide, better knowledge about long-term outcomes and risks of kidney donation is of great importance. The decision-making process...
to donate a kidney can be complicated and stressful, and transplant centres have a responsibility to provide potential kidney donors with as detailed and accurate information as possible about consequences of nephrectomy, both in the short term and in the long term. The study from Stockholm reported that kidney donors live longer than age-matched controls and that their causes of death are mainly cardiovascular diseases and malignancies [1]. Living donors have traditionally been the preferred choice for patients in need of kidney transplants in Sweden and the Transplant Institute at the Sahlgrenska University Hospital in Gothenburg is one of the largest kidney transplant centres in Europe. The living donor pool initially consisted of parents and siblings, but has expanded over the years to also include more relatives, spouses and friends, and more recently, anonymous donors have also been accepted. Albeit, since Sweden lacks a national consensus for post donation follow-ups, there is a need to investigate donor kidney function over time, and also to explore whether it is related to signs of anaemia or hyperparathyroidism, which is typical for renal insufficiency. Earlier studies from transplant centres have revealed that in the short term kidney function recovers to ~70% of pre-donation GFR [2] and that there is no accelerated loss of kidney function among donors [3]. Moreover, the incidence of end-stage renal disease (ESRD) is typically found to be between 0.2 and 0.6% among large donor populations, which is comparable to that of the general population [4,5]. Here, we conduct a cross-sectional retrospective study to investigate the development of renal function in living kidney donors.

Materials and methods

Study design and donors

The cohort originally consisted of a total of 1110 living donors that were nephrectomized at the Sahlgrenska University Hospital between 1965 and 2005. Of these, 61 donors were living abroad. The largest group of donors from abroad were of Icelandic origin. In addition, 170 donors were deceased and 56 could not be identified due to incomplete social security numbers, leaving 823 donors available for the study. These were invited to participate in the study by mail, and the study was also advertised through the Swedish kidney patients’ association magazine. Approval for the study was obtained from the Regional Ethics Committee in Gothenburg to cover all donors in Sweden. In total, 573 donors agreed to participate and underwent follow-up medical examinations between 2007 and 2009. These included measurements of height, weight, blood pressure (BP) and registration of antihypertensive treatment. Lab tests included s-creatinine, s-urea, s-albumin, b-haemoglobin (Hb), s-parathyroid hormone (PTH), measured glomerular filtration rate (mGFR) with iohexol clearance or Cr-EDTA clearance, urine albumin excretion and urine albumin/creatinine ratio. In cases where extremely abnormal results were discovered, donors were referred to their local physician for further evaluation. Modified Diet in Renal Disease (MDRD) (creatinine-based, four-factors equation) was used to calculate estimated glomerular filtration rate (eGFR). Previous studies have demonstrated that GFR in healthy Swedish people decreases annually by 1 mL/min from age 50 and upwards [6,7]. Donor kidney function in our cohort was compared with donor kidney function of these previous studies. Either iohexol clearance or Cr-EDTA clearance was used for mGFR since they correlate exceptionally well [8].

Statistical methods

Mean values, standard deviations (SDs) and confidence intervals (CIs) were calculated using conventional methods. Student’s t-test and chi-square were used for a brief comparison between groups. Pitman’s test was applied to test correlations between different variables [9]. This is a non-parametric test for correlations not based on ranks but on the original values. Pearson’s correlation coefficients were calculated. Multivariable regression analyses were used to investigate the relationship between different variables (dependent ones) and current age and time since donation (independent ones). To study relationships between the two GFR variables, and current age and time since donation in further detail, we transformed the GFR variables to normally distributed variables by the transformation \( \Phi^{-1}(F(x)) \), where \( \Phi^{-1} \) is the inverse of the normalized normal distribution function, and \( F \) is the empirical distribution function of GFR. Multivariable regression analyses were then applied with the transformed values as dependent variables and with age and spline functions of time since donation as independent variables [10]. The interaction between age and time since donation was also included in the model. Spline functions were used to obtain smooth curves with a great freedom of variation with time since donation. Mean values were transformed back to the median of GFR. Two-tailed P-values were used.

Results

Characteristics of the donor cohort

Characteristics of the 823 donors invited to participate in this study were as follows: mean age (SD) at time of donation was 47 (11) years, ranging from 20 to 74 years. The current mean age of the donors was 61 (13) years, ranging from 24 to 92 years, and 59% of the donors were female. Mean time since donation at the time of the medical fol-
low-up examination between 2007 and 2009 was 14 (9) years, ranging from 2 to 43 years. Characteristics of the 573 participating donors are listed in Table 1. The current mean age of the donors was 62 (12) years, ranging from 24 to 92 years. Fourteen per cent of the donors (76/538) were considered obese by having a body mass index >30. Mean time since donation was 15 years, ranging from 2 to 43 years. Thus, with respect to age and time since donation, the donor group that agreed to undergo the medical follow-up examination was essentially the same as the whole group. Moreover, at the time of the medical follow-up examination, one donor was in dialysis and another two donors had received kidney grafts. The origins of these cases of kidney disease were chronic glomerulonephritis, nephrosclerosis and renal carcinoma, respectively. The Swedish Renal Registry (SRR, http://www.sronline.se), which handles dialysis and kidney transplantations in Sweden, did not reveal additional donors of the cohort on renal replacement therapy. However, considering all 1100 donors of the original cohort, we found that four donors had died from diagnosed ESRD between 18 and 26 years after donation. Of these, three were diagnosed with nephrosclerosis and one with postrenal failure. Two were on dialysis.

Table 2. Multiple regression analysis with current age and time since donation as independent variables

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variables</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>Current age, Time since donation</td>
<td>0.0157, -0.0086</td>
<td>0.0102, 0.0133</td>
<td>0.1239, 0.5161</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Current age, Time since donation</td>
<td>0.5244, -0.5080</td>
<td>0.0986, 0.1313</td>
<td>0.0000***, 0.0001***</td>
</tr>
<tr>
<td>Urea</td>
<td>Current age, Time since donation</td>
<td>0.0629, -0.0235</td>
<td>0.0068, 0.0091</td>
<td>0.0000***, 0.0097**</td>
</tr>
<tr>
<td>Albumin</td>
<td>Current age, Time since donation</td>
<td>0.0460, 0.0301</td>
<td>0.0181, 0.0243</td>
<td>0.0110*, 0.2148</td>
</tr>
<tr>
<td>Hb</td>
<td>Current age, Time since donation</td>
<td>0.1656, 0.1196</td>
<td>0.0482, 0.0625</td>
<td>0.0006***, 0.0558</td>
</tr>
<tr>
<td>Iohexol/Cr-EDTA</td>
<td>Current age, Time since donation</td>
<td>-0.8147, 0.4142</td>
<td>0.0936, 0.1304</td>
<td>0.0000***, 0.0015**</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>Current age, Time since donation</td>
<td>0.5267, 0.2762</td>
<td>0.0684, 0.0909</td>
<td>0.0000***, 0.0024**</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Current age, Time since donation</td>
<td>0.0333, 0.1064</td>
<td>0.0412, 0.0547</td>
<td>0.4193, 0.0518</td>
</tr>
<tr>
<td>Urea–albumin excretion (mg/L)</td>
<td>Current age, Time since donation</td>
<td>0.5830, 4.8336</td>
<td>1.0786, 1.3522</td>
<td>0.5889, 0.0004***</td>
</tr>
<tr>
<td>Urea–albumin/creatinine (g/mol creatinine)</td>
<td>Current age, Time since donation</td>
<td>0.1536, 0.6406</td>
<td>0.1854, 0.2404</td>
<td>0.4075, 0.0077**</td>
</tr>
<tr>
<td>eGFR</td>
<td>Current age, Time since donation</td>
<td>-0.6559, 0.8274</td>
<td>0.0571, 0.0764</td>
<td>0.0000***, 0.0000***</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01, ***P < 0.001. SE, Standard error.

Estimated and mGFR values correlate strongly

Table 1 lists results of the follow-up medical examination. Mean s-creatinine was 94 (25) μmol/L, ranging from 48 to 383 μmol/L. Mean s-urea was 6.8 (1.8) mmol/L, ranging from 1.8 to 18.4 mmol/L. mGFR by iohexol clearance or Cr-EDTA clearance had a mean value of 68 (15) mL/min/1.73m² body surface, ranging from 25 to 111 mL/min/1.73m² body surface. Mean eGFR using MDRD was 71 (16) mL/min/1.73m² body surface. There was a strong correlation between eGFR and mGFR (P < 0.001, r = 0.583, 95% CI 0.48–0.67). Multivariable regression analyses revealed that there was a negative correlation (P < 0.001) between age and mGFR as well as between age and eGFR (Table 2). At the same time, there were positive correlations between age and s-urea (P < 0.001) and between age and s-creatinine (P < 0.001).
**Renal function improves for several years following donation**

Statistical analyses further reveal that the development of renal function improves for several years following donation. This phenomenon is expected to apply to all donors irrespective of gender and age at the time of donation (Figure 1). After the years of increased renal function, a phase of progressively decreasing kidney function begins, which appears to be more pronounced in the elderly. This decrease in kidney function is somewhat more apparent from kidney development curves based on mGFR (Figure 2) in comparison to kidney development curves based on eGFR (Figure 1). Using multivariable regression analysis, we also found positive correlations between time since donation and mGFR (P = 0.028) as well as between time since donation and eGFR (P < 0.001) (Table 2). In keeping with these findings, both s-creatinine (P < 0.001) and s-urea (P = 0.010) decrease with time since donation. There is no significant difference between men and women in development of renal function.

**One in five kidney donors have microalbuminuria**

We found that 21% (100/471) of the participants had urine albumin/creatinine ratios ≥ 3.0 g alb/mol creatinine and 13% (59/471) of the participants had urine albumin/creatinine ratios ≥ 5.0 g alb/mol creatinine. Urine albumin excretion and urine albumin/creatinine ratios did not reveal a correlation with actual donor age. Albeit we found that urine albumin excretion (P < 0.001) and higher albumin/creatinine ratio (P = 0.008) increases with time since donation (Table 2).

**Low Hb levels correlate strongly with low-estimated GFR**

Hb levels were measured in 502 donors. Mean Hb was found to be 142 (11) g/L, ranging from 101 to 180 g/L. Regression analyses revealed a negative correlation between Hb and age (P < 0.001) (Table 2) as well as a strong positive correlation between Hb and eGFR (P < 0.001) (Table 2). Hb levels did not correlate with time since donation. According to the WHO definition of anaemia, corrected with Nilsson-Ehle results for elderly people [11], we found a total of 12 (2.1%) anaemic donors.

**Donors with lower eGFR have higher levels of PTH**

PTH was determined in 423 donors. Mean PTH was found to be 5.2 (2.2) pmol/L, ranging from 0.32 to 13.8 pmol/L, and 20% of the donors were above the recommended upper reference PTH limit of 6.90 pmol/L. Regression analyses revealed that PTH levels neither correlated with actual donor age nor correlated with time since donation (Table 2). However, Pitman’s test revealed a correlation between PTH and eGFR (P < 0.05) with lower eGFR correlating with higher PTH, indicative of secondary hyperparathyroidism.

**Serum albumin levels decease with age**

s-Albumin levels were measured in 511 donors. Mean s-albumin was found to be 41 (4.4) g/L, ranging from 24 to 96 g/L. In total, 22 (4.3%) of the donors had values below the recommended lower reference s-albumin concentration of 36 g/L. Multivariable regression analyses revealed that s-albumin levels significantly decreases with age (P = 0.011) but that s-albumin levels do not correlate with time since donation (Table 2).

**Almost half of the kidney donors suffer from hypertension**

At the time of the medical follow-up examination, 23% (126/546) of donors were on antihypertensive medication. An additional 22% (117/543) of the donors were found to suffer from hitherto undiagnosed hypertension (BP >140/90 mm Hg) and were not on antihypertensive medication at the time of the medical follow-up examination. Statistical analyses reveal that systolic BP increases with both time since donation (P = 0.002) and age (P < 0.001) (Table 2).

**Discussion**

This large cross-sectional retrospective study of kidney donors from a single transplant centre reveals that kidney function improves for many years following donation, and so delays the ageing process. The first study to report that renal function of the remaining kidney in living donors improves with time came from the Swiss Donor Registry [12]. However, the current study also identifies donors with ESRD related to the remaining kidney. One case each of glomerulonephritis, nephrosclerosis and renal cancer corresponds to an ESRD incidence of 0.4% for our cohort, which is in line with that of the general public. In comparison to the Swiss Donor Registry study, the cohort of this study is an ageing donor group. The mean age was 61 years, with the oldest donor being 94 years, at the time of the medical follow-up examination. Younger donors exhibit a capacity for hyperfiltration that remains for several years, whereas renal function declines in the elderly. This age-related difference is more evident from mGFR than from eGFR and may suggest that age per se should constitute a more pronounced selection criterion for potential kidney donors. A recent study from Minneapolis also demonstrated that kidney function improves with time since donation [13], but an age-dependent decline in renal function could not be identified in the younger cohort of that study. A study from Stockholm, investigating renal function in parents who have donated a kidney to their children, also revealed stable and good kidney function among a younger cohort [14], in particular for female donors, although in the study presented here, we did not find a significant difference between the sexes with regard to development of renal function.

We also demonstrated increasing microalbuminuria over time since donation, presumably due to the hyperfiltration effect. A previous meta-analysis of kidney donors has demonstrated that proteinuria increases with time since donation [15], but proteinuria is unspecific, whereas albuminuria is a specific measurement of glomerular function/load. Moreover, microalbuminuria is associated with an increased risk of cardiovascular disease [16]. Whether this applies to kidney donors remains to be investigated.

So far, changes in Hb or erythropoietin levels following nephrectomy has not been reported among kidney donors.
Renal function in living kidney donors

17, although it should be noted that in previous studies the maximum average observation time has never exceeded 11 years. The average observation time of our study is substantially longer. In addition, the cohort contains donors with observation times of >40 years, and we do find that Hb levels decrease with both increasing age and decreasing renal function. Elevated PTH levels were not associated with age but with lower renal function. A previous study reported signs of hyperparathyroidism among 19% of kidney donors [18], but it remains unclear whether this was associated with renal function. Taken together, our results indicate that it may be useful to measure Hb and PTH in the event of kidney donor long-term follow-up medical examinations, though it should be noted that our study did not identify eGFR cut-off levels for anaemia or hyperparathyroidism.

The study presented here covers a comparatively long period of 40 years, and there is a possibility that changes in kidney donor selection criteria have influenced the results. The basic principle has been, and still is, that a donor should be a healthy person without chronic diseases, hypertension, albuminuria or signs of kidney disease and not taking medication. The investigation program has included measurements of renal function with injection technique and now also includes thrombosis risk tests. The GFR limit has been increased from >65 to >80 mL/min/1.73m² body surface. Thus, kidney donor selection criteria have become more restrictive during the 40 years of this study and not the other way round.

Strengths of this study are the long observation time, the large and homogeneous donor group and the fact that actual renal function was measured in one-third of the donors, which we consider a relatively large number. Limitations of the study are that data are based on single medical follow-up examinations, that many tests were conducted using local laboratories to ensure a high participation rate and that the study is not prospective. However, a recent prospective study from the Netherlands indicates that the renal function of the remaining kidney increases from 2 months to 6 years following nephrectomy [19], supporting the results of this retrospective study.

In conclusion, our study demonstrates that renal function of the remaining kidney in living donors improves for many years but that it will show signs of slight deterioration in the longer run. We also found that microalbuminuria and hypertension increases with time since donation. Creatinine analysis are unwarranted in the long term but should be offered to donors that request them and on clinical grounds, and the observation that 22% of the donors suffered from previously undiagnosed hypertension suggests that regular BP controls may be useful. However, provided strict donor selection criteria are applied, regular medical follow-up examinations are likely superfluous in the long term and can potentially be offered only to donors that request them provided donor selection criteria continue to be strict.

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Conflict of interest statement. None declared.

(See related article by Steiger. Why did mother nature provide us with two kidneys? Nephrol Dial Transplant 2011; 26: 2076–2078.)

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