Long-term follow-up of kidney donors: a longitudinal study

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Abstract

Background. Kidney donors are not adversely affected by compensatory hyperfiltration of the remaining kidney in the early years after nephrectomy, but long-term longitudinal studies are lacking.

Methods. The renal function and blood pressure of 75 donors was evaluated in 1984, 1.4–20.7 years after surgery. Forty-seven of the original cohort (23 male, age 38–80 years) underwent repeat study a decade later (12–31 years post-nephrectomy), using identical laboratory techniques.

Results. Glomerular filtration rates (GFR) as measured by $^{51}$Cr EDTA clearance was relatively unchanged a decade later with 41 of 47 subjects (87%) having EDTA clearance within the normal laboratory reference range at review. The change in GFR in the remaining six subjects was statistically not significant. No correlation between GFR and time after nephrectomy was undertaken. Albumin excretion rate (AER), on timed overnight urine collections, was increased (>20 mg/min) in 16 subjects (34%), although 14 of these individuals were also hypertensive. The prevalence of hypertension was significantly increased compared with age/sex matched data from epidemiological studies of the general population (both in the UK and the US), especially in those over the age of 55 years.

Conclusion. This study demonstrates that the function of the solitary kidney is not adversely affected by prolonged compensatory hyperfiltration, although there appears to be an increased prevalence of microalbuminuria and hypertension. Regular follow-up of kidney donors is recommended in order to manage their complications effectively and to detect hypertension and or renal impairment early in those who may develop it.

Key words: kidney donors; blood pressure; glomerular filtration rate; creatinine clearance; microalbuminuria

Introduction

The importance of living kidney donors cannot be underestimated, especially in the context of a worldwide shortage of donor organs. There is good evidence that long-term graft survival is superior when living donors are used [1] and a more recently published study suggests that even living unrelated spousal donors may result in a comparable outcome [2].

The long-term prognosis of kidney donors has long been a subject of concern and debate. This was based on the reports in the 1980s which suggested that in the experimental animal surgical ablation of functional renal mass results in progressive hyperfiltration-mediated structural damage to the remaining nephrons [3,4]. Subsequently a substantial number of follow-up studies of individuals with a single kidney have been undertaken. These have been critically reviewed [5,6] and more recently subjected to meta-analysis [7]. Data thus far available supports the relative safety of kidney donation, both in the short and long term. However, there is sparse data beyond two decades following donor nephrectomy. Moreover, all conclusions have been based on cross-sectional studies [7] and include several causes of reduced renal mass such as unilateral renal agenesis, unilateral nephrectomy for renal disease, and donor nephrectomy.

We report a single-centre longitudinal long-term follow-up study of kidney donors from the northeast of England, UK. Results of the initial cross-sectional analysis of the original cohort of 75 individuals has been previously published [8].

Subjects and methods

Donor nephrectomy was performed on 92 individuals at the University of Newcastle upon Tyne, UK, between March 1963 and June 1982. Seventy-five donors were studied in 1983–84 with respect to their blood pressure, renal function (measured by single-shot $^{51}$Cr EDTA clearance) and urinary albumin excretion rates [8].

The aim of the present study was to recall as many subjects from the original cohort studied in 1984 and to re-evaluate them clinically and with identical laboratory techniques. Seventy donors were contacted by post (since we were aware
of five deaths in the original cohort). The details of the response to the initial postal request are outlined in Table 1. We eventually studied 47 subjects (23 male and 24 female) from the original cohort of 75 studied in 1984. Informed consent was obtained from all those studied. A total of seven subjects had died since the first evaluation. The individual causes of death are listed in Table 2. One patient had previously reached end-stage renal failure 13 years after donating a kidney to his brother. His case was reported elsewhere [9], and is not included in the present analysis.

Forty-four subjects were studied in outpatient clinics in the vicinity of their residences, while three preferred to be evaluated in their homes. All 47 subjects were interviewed, and physical examination performed. Three resting blood pressure readings in the supine, sitting, and erect postures were taken using a random-zero mercury sphygmomanometer. The diastolic pressure was taken at the fifth phase of Korotkoff. The arithmetic mean of these three readings was taken as the current blood pressure. To determine the prevalence of hypertension, any of the following criteria were utilized [10]: diastolic blood pressure of 90 mmHg or more, systolic blood pressure of 140 mmHg or more, or current use of antihypertensive drugs prescribed by the individual’s general practitioner, regardless of actual blood pressure measurement. In the latter instance the general practitioner was contacted to ensure that pretreatment blood pressure measurements had complied with the above definitions of hypertension. Similarly, all donors found to be hypertensive during the study were reviewed by their general practitioners and in all cases hypertension was confirmed and appropriate therapy commenced.

All 47 subjects submitted two timed overnight collections of urine for the determinations of albumin excretion rate. All samples were analysed in one batch at a central biochemistry laboratory with standardized assays after initially being frozen at −40 °C soon after collection [11,12]. Venous blood was drawn for routine laboratory studies including plasma urea, creatinine, glucose, albumin, and complete blood counts.

$^{51}$Cr EDTA was administered intravenously to each donor in a standard dose of 2.2 MBq (60 µCi) after taking a baseline serum sample, and venous blood drawn from the opposite arm at 120 and 240 min after the injection to determine the fall in radioactivity. GFR was estimated as previously described [13]. Values for EDTA clearance were corrected for body surface area (ml/min/1.73 m²).

Urinary albumin was measured on each timed overnight collection using a single antibody radioimmunoassay as previously described [8]. The result was expressed as the arithmetic mean of the two values.

**Statistical analysis**

Data was analysed using the Statistical Analysis System. In the text measurements are expressed as the mean ± standard deviation. The correlations of the most recent $^{51}$Cr EDTA clearance and albumin excretion rate with time since nephrectomy were determined.

We compared the prevalence of hypertension in this group of subjects (Caucasians from the north of England, UK) with the reported prevalence of hypertension in the Newcastle area (‘Whickham Study’ [Vanderpump et al., Personal communication]) and that given in the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1991 reported recently [14]. The statistical test done to compare the proportions of hypertensives in the donor group to that of the ‘normal’ group was a Cochran—Hantzel test which allows stratification by age and sex. Similarly the data on $^{51}$Cr EDTA clearance was compared to data available from the literature analysing age-related changes in renal function in a normal Caucasian population [15]. The chi-square test was used to compare the proportion of individuals within normal limits for the donors and controls, with control values determined from the literature.

**Results**

There were 23 males and 24 females. The mean age of the entire group was 64 ± 9 years; range 38–80. The mean duration since nephrectomy was 19.6 ± 5.0 years, range 12.5–31. Twenty-three donors were now more than 20 years post-nephrectomy (13 males, 10 females).

Two subjects had not been studied in 1984 (one of them had then refused participation and the other was untraceable at the time). Their data has been used for prevalence analysis for 1994 but not for comparison with 1984 data.

The scatter seen in Figures 1 and 2 is consistent with the fact that there was no significant correlation between current $^{51}$Cr EDTA clearance, albumin excretion rate, and the years since donation (Pearson’s correlation coefficient $r = −0.02$ and 0.02 respectively). This held true even after including age as a covariate factor.

$^{51}$Cr EDTA clearance

Using the 1981 paper by Granerus and Aurell [15], we found the upper and lower limits of $^{51}$Cr EDTA clearance for a given age. Ninety-five percent of subjects should have values within these limits. The values from the graph in the paper were read and the equation of the line shown in the graph was determined. A plot of the normal limits and the observed EDTA clearance values for each individual on the latest assessment was made. One can see from this plot (Figure 3) that most
The statistically significant indication that the proportion of kidney donors with an EDTA clearance within normal limits may be somewhat lower than a normal or healthy population with two kidneys.

Table 3 shows the data on the six patients whose $^{51}$Cr EDTA clearance fell below the lower limit of normal for age at the current assessment. The age in 1994 of these six patients ranged from 65 to 80 years and they were 13–25 years post-donor nephrectomy (mean 19 years ± 5.9). There were five females and one male. The mean GFR in 1984 was 56 ± 13.7 ml/min/1.73m$^2$ and 45 ± 7.61 ml/min/1.73m$^2$ in 1994. The change in GFR had a mean of 10.7 and a median of 6.5 which is not significantly different from zero (Wilcoxon’s signed rank test, $P$ value 0.3125). The albumin excretion rate was higher for all six subjects.

Figure 4 shows EDTA clearance in 1994 of all kidney donors studied plotted against the corresponding values in 1984. Most values fall around the line of identity, indicating that there was no substantial change in the EDTA clearance over 10 years in these subjects. In fact on examining the data closely there was actually a small but significant increase in EDTA clearance in 1994 compared to that in 1984 (paired t test; $P=0.03$, median difference = 4 ml/min/1.73m$^2$; mean difference = 5.97ml/min/1.73m$^2$ ± 17.55).

**Albumin excretion rate**

There were 16 (13 males and 3 females) subjects (34%) with AER above 20 μg/min. This was highly significant ($P=0.0003$) when compared to a control group where none of the 31 subjects studied had an AER above 20 μg/min [16]. The mean AER in donors was 22.5 μg/min ($±$ 35.64, range 1.41–197.80). None of the patients had macroalbuminuria. Figure 5 shows the changes that occurred over 10 years in these subjects (median increase = 2.7, $P<0.001$, signed rank test). Table 4 shows data on the 16 subjects that were noted to have microalbuminuria in 1994. The mean AER among them was 11.8 ± 7.43 μg/min (1.4–26.7) in 1984 and had increased to 56.9 ± 44.3 μg/min (20.6–197.8) in 1994 ($P<0.0001$, signed rank test). The mean EDTA clearance in the same subjects had changed from 69.9 ± 17.4 ml/min/1.73 m$^2$ to 74.6 ± 24.7 ml/min/1.73 m$^2$. This was not statistically significant ($P=0.40$, signed rank test).

**Blood pressure**

Thirty-five donors (74.5%) were hypertensive in 1994 compared to 36% in 1984. Reference groups were derived from the Whickham Study [Vanderpump et al., Personal communication] and the NHANES III [14], where prevalence of hypertension by gender and age group are given. In Figure 6 the open circles show the prevalences reported for males in the Whickham Study
Table 3. Kidney donors with GFR lower than predicted at 10-year follow-up

<table>
<thead>
<tr>
<th>Donor</th>
<th>Age</th>
<th>Sex</th>
<th>Years since donation</th>
<th>GFR P (EDTA clearance) pre-nephrectomy</th>
<th>GFR 1, GFR (EDTA clearance) in 1984 a.e.r.</th>
<th>GFR 2, GFR (EDTA clearance) in 1994 a.e.r.</th>
<th>BP P, Blood pressure pre-nephrectomy</th>
<th>BP 1, Blood pressure in 1984</th>
<th>BP 2, Blood pressure in 1994</th>
<th>CC, Comorbid condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>70</td>
<td>F</td>
<td>15 NA</td>
<td>41</td>
<td>45</td>
<td>NA</td>
<td>2.1</td>
<td>4.25</td>
<td>160/90</td>
<td>172/87*</td>
</tr>
<tr>
<td>RP</td>
<td>71</td>
<td>F</td>
<td>13 NA</td>
<td>41</td>
<td>40</td>
<td>NA</td>
<td>8.8</td>
<td>50.3</td>
<td>130/85</td>
<td>149/82</td>
</tr>
<tr>
<td>MB</td>
<td>65</td>
<td>F</td>
<td>25 NA</td>
<td>71</td>
<td>44</td>
<td>NA</td>
<td>0.86</td>
<td>2.98</td>
<td>140/80</td>
<td>191/104</td>
</tr>
<tr>
<td>ER</td>
<td>77</td>
<td>F</td>
<td>24 NA</td>
<td>67</td>
<td>55</td>
<td>NA</td>
<td>1.36</td>
<td>2.56</td>
<td>140/90</td>
<td>127/81</td>
</tr>
<tr>
<td>DA</td>
<td>72</td>
<td>F</td>
<td>13 NA</td>
<td>30</td>
<td>53</td>
<td>NA</td>
<td>19.6</td>
<td>73.4</td>
<td>150/80</td>
<td>159/100</td>
</tr>
<tr>
<td>GH</td>
<td>80</td>
<td>M</td>
<td>24 NA</td>
<td>66</td>
<td>35</td>
<td>NA</td>
<td>41.6</td>
<td>82.14</td>
<td>114/72</td>
<td>145/58</td>
</tr>
</tbody>
</table>

while the open triangles show the prevalences reported in the NHANES III. Logistic regression was used to estimate the prevalence (or probability) of hypertension among donors as a function of age. The open squares show the fitted (estimated) values corresponding to the ages of the donors. Figure 7 shows the same information for female donors. From the graphs it would appear that the difference between the estimated donor curve and the reference groups becomes more pronounced with age. It is pertinent to note that all 14 of the men over the age of 55 years were hypertensive, as were 12 of the 13 women donors who were over 55. A Cochran—Mantel—Haenszel test was used to compare the proportion of hypertensives in the donor group to the proportions for normals reported by the Whickham Study. This test allows for stratification by age group and sex. The P value for the test was <0.001. This is evidence that the prevalence of hypertension in the cohort of kidney donors studied is significantly higher than in the referenced normal controls.

**Age and donor nephrectomy**

We used a multiple regression analysis to look at the influence of age at the time of donor nephrectomy and years since donation in relation to rate of change in EDTA clearance over the 10 years that these patients were studied. It was determined that the estimated change in EDTA clearance is about 1.0 ml/min/1.73 m² smaller for each year of age at donation, as the subjects became older. It was also estimated that the change in EDTA clearance is smaller by 1.5 ml/min/1.73 m² for each year since donor nephrectomy. In summary, the estimated multiple regression relationship is as follows:

\[ \Delta \text{EDTA} = 80.4 - 1.0 (A_d) - 1.5 (Y_d) \]

where \( \Delta \text{EDTA} \) is the change in \( ^{51}\text{Cr} \text{EDTA} \) clearance over the 10 years that these patients were studied, \( A_d \) is the age at donation, and \( Y_d \) are the number of years since donation.
Table 4. Kidney donors with microalbuminuria at 10-year follow-up

<table>
<thead>
<tr>
<th>Donor</th>
<th>Age</th>
<th>Sex</th>
<th>Yd</th>
<th>a.e.r.1</th>
<th>a.e.r.2</th>
<th>BP Pre</th>
<th>BP 1</th>
<th>BP 2</th>
<th>GFR 1</th>
<th>GFR 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI</td>
<td>69</td>
<td>M</td>
<td>23</td>
<td>26.7</td>
<td>197.8</td>
<td>150/80</td>
<td>168/104</td>
<td>158.94*</td>
<td>81</td>
<td>61</td>
</tr>
<tr>
<td>DR</td>
<td>56</td>
<td>M</td>
<td>24</td>
<td>19.7</td>
<td>32.64</td>
<td>160/74</td>
<td>130/99</td>
<td>127.84*</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>GT</td>
<td>68</td>
<td>M</td>
<td>24</td>
<td>14.6</td>
<td>21.31</td>
<td>NA</td>
<td>153/93</td>
<td>142/66</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>DL</td>
<td>71</td>
<td>M</td>
<td>16</td>
<td>NA</td>
<td>91.0</td>
<td>NA</td>
<td>NA</td>
<td>154/67</td>
<td>NA</td>
<td>78</td>
</tr>
<tr>
<td>MB</td>
<td>53</td>
<td>M</td>
<td>22</td>
<td>NA</td>
<td>24.71</td>
<td>135/85</td>
<td>122/83</td>
<td>127/83</td>
<td>57</td>
<td>101</td>
</tr>
<tr>
<td>WC</td>
<td>72</td>
<td>M</td>
<td>17</td>
<td>13.7</td>
<td>75.36</td>
<td>120/80</td>
<td>132/78*</td>
<td>171.86*</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>GT</td>
<td>68</td>
<td>M</td>
<td>24</td>
<td>9.94</td>
<td>20.63</td>
<td>140/90</td>
<td>136/89</td>
<td>163/43</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>GG</td>
<td>65</td>
<td>M</td>
<td>15</td>
<td>20</td>
<td>22.61</td>
<td>120/80</td>
<td>137/104*</td>
<td>141/78</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>RD</td>
<td>72</td>
<td>M</td>
<td>23</td>
<td>4.26</td>
<td>61.06</td>
<td>120/80</td>
<td>120/81</td>
<td>154/91</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>MS</td>
<td>68</td>
<td>M</td>
<td>25</td>
<td>6.2</td>
<td>45.23</td>
<td>130/85</td>
<td>133/72</td>
<td>151/96</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>HN</td>
<td>70</td>
<td>M</td>
<td>16</td>
<td>1.4</td>
<td>54.61</td>
<td>130/80</td>
<td>136/80</td>
<td>141/63</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>GH</td>
<td>80</td>
<td>M</td>
<td>24.5</td>
<td>10.4</td>
<td>82.14</td>
<td>NA</td>
<td>114/72</td>
<td>145/58</td>
<td>66</td>
<td>35</td>
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<tr>
<td>IM</td>
<td>66</td>
<td>F</td>
<td>21.5</td>
<td>2</td>
<td>27.1</td>
<td>130/85</td>
<td>132/91*</td>
<td>157/73*</td>
<td>85</td>
<td>72</td>
</tr>
<tr>
<td>DA</td>
<td>72</td>
<td>F</td>
<td>13</td>
<td>18.1</td>
<td>73.36</td>
<td>150/85</td>
<td>159/100</td>
<td>194/92</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>RP</td>
<td>71</td>
<td>F</td>
<td>13</td>
<td>8.8</td>
<td>50.29</td>
<td>130/85</td>
<td>149/82</td>
<td>119/41*</td>
<td>41</td>
<td>40</td>
</tr>
</tbody>
</table>

Yd, Years since donation  
BP Pre, Blood pressure pre-donation  
BP 1, Blood pressure in 1984  
BP 2, Blood pressure in 1994  
GFR 1, Glomerular filtration rate (EDTA clearance) in 1984  
GFR 2, Glomerular filtration (EDTA clearance) in 1994  
a.e.r. 1, Albumin excretion rate in 1984  
a.e.r. 2, Albumin excretion rate in 1994  
On antihypertensive medication.

Discussion

We have reported a single-centre experience in the long-term follow-up of kidney donors. To our knowledge, this is the first longitudinal follow-up data on a cohort of donors previously studied and reported 10 years ago [8]. Most of the studies done so far have been cross-sectional [7], and do not have paired data on the same group of patients at different times after donor nephrectomy.

We used the single-shot 51 Cr EDTA method, which is an efficient technique for the estimation of GFR [17]. Judging by the Cr EDTA data, we found that GFR is reasonably well preserved in kidney donors over 2–3 decades post-nephrectomy. Indeed, it is comparable to the GFR in normal individuals of the same age and sex in a reference population [15]. Six donors (12.2%) (Table 3) had a GFR that had fallen below the normogram (Figure 3) that predicts GFR for age in individuals with two kidneys. This may apparently be of concern. However, a closer analysis revealed that in fact there had been no statistically significant change in GFR in these individuals over the period of observation. Thus they had probably started with a lower GFR, which had then remained relatively stable over the next decade (1984–1994). Since we do not have precise measurement of their GFR pre-nephrectomy it is impossible to determine to what extent their renal function declined, if at all, between the time of nephrectomy and 1984. Overall, these results are quite reassuring, and consistent with data reported in the literature [7,18]. When we compared the EDTA clearance in 1994 to that in 1984 in the subjects studied, we found that in fact there was a median increase of 8 ml/min/1.73 m² (although admittedly there was a wide scatter of values around the mean). This was statistically significant and may reflect that compensat-
ory mechanisms may be at play even beyond two decades after nephrectomy. The mean EDTA clearance in 1994 was 76.5 ± 19 versus 70 ± 16 ml/min/1.73 m² in 1984 in the subjects studied.

There was an increased prevalence of microalbuminuria in the group of donors studied. However, none of the donors had macroalbuminuria. There had been a significant increase in the albumin excretion rate over the 10-year follow-up period. We are unable to offer a clear explanation for the apparent male preponderance (almost 4:1) in the subgroup of patients (Table 4) with increased AER. There was no correlation between time after nephrectomy and the present AER (Figure 2). Fourteen of the 16 subjects with increased AER were hypertensive at current evaluation in 1994 and only five among these were on antihypertensive medications. Thus it is tempting to speculate that hypertension may itself be responsible for the increase in AER. We have not attempted, at this stage, to investigate whether the albuminuria may be in some way related to the renal disease in the recipient and therefore may be familial, although this seems unlikely as none of the donors had macroalbuminuria.

An increased prevalence of hypertension was a striking finding of this study. The number of donors predicted to be hypertensive on the basis of analysis of epidemiological data [14] was 24/47. The actual number found hypertensive was 35/47. Unfortunately, less than half (13) of hypertensive donors were on therapy. The data on hypertension is at variance with many studies in the literature which indicate that the incidence of hypertension is no different from controls [7]. It is interesting to note that the prevalence curves (Figures 6 and 7) of hypertension in both men and women were similar in the north of England compared to the NHANES III derived data from the United States. There is certainly the possibility that an increased prevalence of hypertension in the studied donor group has a familial basis but as we did not use siblings as controls in making comparisons, this is an open-ended issue that cannot be answered on the basis of our study.

From a regression analysis of the data, it seems that the younger one is at the time of nephrectomy, the greater the subsequent increase in GFR. For example, using the multiple regression equation shown earlier, we can compute that if an individual is 25 years of age at the time of nephrectomy, his GFR is expected to increase by 37 ml/min/1.73 m² after 12 years. On the other hand, a 50-year-old's GFR rises by only 0.4 ml/min/1.73 m² after 20 years post-donation. This should not be taken to mean that age in isolation should be a factor in the decision-making process prior to considering an individual for donor nephrectomy.

We did not find any of our results significantly different in the female donors in our study group except the observation that in the group of subjects with increased AER there was a male preponderance of uncertain significance. One study has suggested that gender, in addition to age, is a significant predictor of renal function after renal donation [19] and that older women may be at a higher risk than men of an adverse effect on renal function following donor nephrectomy.

In conclusion, renal function seems relatively well preserved in kidney donors 20–30 years on. This information will be reassuring for potential donors. The increased incidence of microalbuminuria and hypertension as in our study group, though of concern, is not by itself alarming. However, it calls for a more systematic follow-up policy of kidney donors, which unfortunately is not standard practice. We remain cautiously optimistic about the long-term prospects of kidney donation at least to the end of the third decade after the operation, provided selection criteria [20] are stringently adhered to, and regular follow-up is ensured.

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