Risk of Live Kidney Donation- Indian Perspective
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Abstract
Introduction: Live kidney donation is an established form of organ donation but carries the risk of an unnecessary surgery in a normal individual for the benefit of the recipient. Long term effects of nephrectomy have not been studied in Indian donors so far.

Aim: The aim of this pilot study was to review the effects of kidney donation on morbidity (renal function, BP and proteinuria), psychosocial outcome and mortality.

Material and Methods: Fifty donors who had nephrectomy 3 months to 20 years prior formed the material of this study. Medical history (donor age at nephrectomy, duration post-nephrectomy, family history), physical examination including anthropometry and systolic and diastolic blood pressure (SBP and DBP) measurement pre and post nephrectomy were recorded. Evaluation of renal function included pre and post-nephrectomy urinalysis, determination of microalbuminuria, serum creatinine, blood urea, 24 hr urinary protein and creatinine estimation and calculation of creatinine clearance. Renal length was measured by ultrasonography. Quality of life (QOL) was assessed by a standard questionnaire. Donors with co-morbidities not related to nephrectomy were excluded from the analysis. Data was statistically analyzed.

Results: Twenty two donors (44%) were males and 28 (56%) females. Parents constituted the majority 39 (78%); 10 were siblings (20%) and 1 was a spousal donor. The mean age at donation was 41.26 ± 8.12 years (25-54.16 years). Since kidney donation a mean time interval of 63 months (3-264 months) had elapsed. There was a mean rise of 9.96 mm Hg in SBP and 7.18 mm Hg in DBP. Hypertension was noted in 23 (46%). 20 donors (40%) developed microalbuminuria (MAU) post nephrectomy and 7 (14%) developed overt proteinuria (>300 mg/day). Mean GFR pre and post nephrectomy was 102.74 ± 6.91 ml/min and 74.54 ± 14.64 ml/min with a mean reduction of 28.2 ± 13.57 ml/min. There was no significant change in serum creatinine after donation (0.97 ± 0.09 mg/dl vs 1.22 ± 0.82 mg/dl). There was an increase in renal length of 1.14 ± 0.73 cm. None of the donors regretted donation.

Conclusion: This pilot study reaffirms the safety of live kidney donation. There was a fall in GFR with consequent increase in renal length postnephrectomy. The long term implications of the minimal increase in proteinuria and rise in blood pressure need to be evaluated in larger cohort of donors over a longer period of time. This study underscores the need for initiating a donor registry to achieve this objective. ©

INTRODUCTION
Renal transplantation using living donors still remains of interest given the shortage of cadaveric donors and the ethical issues of unrelated renal transplant. The frequency of living kidney donation has increased over the past decade in USA and in Eurotransplant countries, currently accounting for 16-17% of the total transplants. In 2001, for the first time, more living donor kidneys than the cadaveric kidneys were transplanted in USA. In India, living kidney donation accounts for >95% of the total number of transplants.

Surgical ablation of the renal tissue in animals leads to compensatory hyperfiltration, hypertension and focal segmental glomerulosclerosis, raising concern in human related transplantation. The detection of microalbuminuria has been shown to predict later more severe renal disease in diabetics and has been identified as an early marker of renal injury. The peri-operative and long term risks of living kidney donation are therefore, of concern and the risk of uni-nephrectomy should not be neglected. There are conflicting reports on the effect of nephrectomy on the renal function. A number of Western studies have reviewed the changes in renal function and blood pressure post-nephrectomy. There is no data on Indian donors in literature. It is documented that Indians differ in presentation and progression of diseases from their Western counterparts. Given this unique genetic background, ethnicity and
environmental factors, there is every reason to believe that the effects of kidney donation could be different in Indians as compared to what is reported from the West.

Aim

The aim of this pilot study was to review the effects of kidney donation on morbidity (renal function, BP and proteinuria), psychosocial outcome and mortality.

MATERIAL AND METHODS

Fifty donors who had nephrectomy at the Osmania General Hospital 3 months to 20 years prior to the study formed the material of this study. Medical history (donor age at nephrectomy, duration post-nephrectomy, relationship to patient, family history of hypertension, diabetes, renal disease, other illnesses) and pre-nephrectomy blood pressure were recorded. Physical examination including anthropometry was done, height was measured on stadiometer and weight was recorded using an electronic weighing scale. Blood pressure was determined using mercury sphygmomanometer in sitting posture after 15-20 min rest; the mean of three readings was taken as per JNC VII guidelines, the disappearance of Koratkkoff sounds taken as the diastolic pressure. Hypertension was defined using JNC VII criteria.4

Evaluation of renal function included pre- and post-nephrectomy urinalysis, determination of microalbuminuria by semi-quantitative strip test by immunoturbidimetric assay, measurement of creatinine by modified Jaffe’s method and urea by urease method. 24 hr urinary protein and creatinine estimation was done by trichloroacetic acid precipitation and Jaffe’s colorimetric method respectively. Creatinine clearance was determined by standard UV/P formula. The reliability of urine collection was assessed by comparing 24 hours urinary creatinine excretion with known levels based on age, sex and weight. Ultrasound abdomen was done pre and post nephrectomy to assess renal size. Quality of life (QOL) was assessed by a standard questionnaire.5

Statistical analysis was done using Student t test for difference between means and chi-square test for proportions and Fischer test for correlation. p value of <0.05 was considered significant.

RESULTS

Demography: Twenty two (44%) were males and 28 (56%) females with a ratio of 1:1.2. Parents constituted the majority 39 (78%) (29 mothers and 10 fathers); 10 were siblings (20%) and 1 was a spousal donor. The mean age at donation was 41.26 ± 8.12 years (25-54.16 years). One donor had hypertension which was well controlled with medications, with no evidence of target organ damage. Family history of hypertension was present in 7 (14%) and family history of diabetes in 5(10%), none had renal disease in the family. Since kidney donation a mean time interval of 63 months (3-264 months) had elapsed (Table 1).

Renal functions - Pre and postnephrectomy: (Table 2)

Hypertension: There was a rise of 9.96 mmHg in mean arterial pressure (p<0.05). Hypertension was noted in 23(46%) post-nephrectomy (p<0.05). All donors with a family history of hypertension became hypertensive post nephrectomy.

Proteinuria: None of the donors had microalbuminuria prenephrectomy, while 20 (40%) developed MAU post nephrectomy (p<0.05). Seven (14%) of the donors developed overt proteinuria (>300 mg/day) (p<0.05).

Glomerular filtration rate (GFR) and kidney length: There was a reduction of 28.2 ± 13.57 ml/min

Table 1: Demographic data

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors</td>
<td>50</td>
</tr>
<tr>
<td>Males</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Females</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Relations</td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>39 (78%)</td>
</tr>
<tr>
<td>Sibling</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Spouse</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Mean age at nephrectomy</td>
<td>41.26 ± 8.12 years (25-54.16 years)</td>
</tr>
<tr>
<td>Mean interval postnephrectomy</td>
<td>63 months</td>
</tr>
<tr>
<td>Mean height</td>
<td>156.35 ± 8.15 cm</td>
</tr>
<tr>
<td>Mean weight</td>
<td>59.48 ± 12.18 kg</td>
</tr>
<tr>
<td>F/H of DM</td>
<td>10%</td>
</tr>
<tr>
<td>F/H of HT</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 2: Pre and post nephrectomy renal functions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prenephrectomy</th>
<th>Postnephrectomy</th>
<th>Difference</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119.8 ± 6.1</td>
<td>129.76 ± 13.84</td>
<td>9.96 ± 12.61</td>
<td>P=ns</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.72 ± 5.72</td>
<td>85.9 ± 9.02</td>
<td>7.18 ± 8.94</td>
<td>P=ns</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>102.74 ± 6.9</td>
<td>74.54 ± 14.64</td>
<td>28.2 ± 13.5</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Proteinuria (mg/24hr)</td>
<td>125.4 ± 25.0</td>
<td>174.22 ± 32.36</td>
<td>48.48 ± 12.6</td>
<td>P=ns</td>
</tr>
<tr>
<td>Kidney length (cm)</td>
<td>9.46 ± 0.39</td>
<td>10.60 ± 0.73</td>
<td>1.14 ± 0.73</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.97 ± 0.09</td>
<td>1.22 ± 0.82</td>
<td>0.45 ± 0.19</td>
<td>P=ns</td>
</tr>
<tr>
<td>Microal positivity (%)</td>
<td>0</td>
<td>40</td>
<td>40</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Overt proteinuria (%)</td>
<td>0</td>
<td>7(14%)</td>
<td>7(14%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1(0.5%)</td>
<td>23(46%)</td>
<td>22(44%)</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>
in GFR after nephrectomy (p<0.05) with no significant change in serum creatinine. There was an increase in renal length of 1.14 ± 0.73 cm (p<0.05), which was significantly greater in females 1.01 ± 0.91 vs 1.25 ± 0.54 cm; (p<0.05).

**Correlation of hypertension and proteinuria:**
Among the various parameters of renal functions a strong correlation was found between hypertension and proteinuria. 5/23 (21.7%) donors with hypertension had proteinuria while only 2/27 (7.4%) without hypertension developed proteinuria. (p<0.05).

**Quality of life (QOL):** The average duration of hospitalisation after surgery was 7.3 ± 1.2 days with 100% donors going back to work within 4 ± 1 weeks. None of the donors regretted donation.

**Co-morbidities:** One donor each, developed hypothyroidism and type 2 diabetes mellitus. There were no donor deaths.

**DISCUSSION**

Living related renal transplant is the preferred treatment for ESRD. Rising number of patients reaching ESRD intensify the demand for expansion of living kidney donor pool. Although the risk benefit ratio for the recipient is very much favourable, the benefit for the donor is much harder to define and is probably very small if pure medical criteria are considered. Nonetheless, non-medical benefits, mostly psychosocial may outweigh the small medical risk. Early renal functional adaptation with no long term ill effects has been documented in most Western studies. Factors such as age, gender and familial predisposition have been known to influence renal function in donors. The paucity of such studies from India prompted us to evaluate the effects of donation on renal functions (BP, proteinuria and GFR), quality of life (QOL) and mortality in our donor population.

**Demography:** Donor sex may influence renal functions. Majority of donors are females. The degree of hypertrophy was significantly greater in males as compared to females (46.9% v/s 26.7%). Nephrectomy is safe in both the sexes and in females nephrectomy is not detrimental to the outcome of pregnancy. In our study females formed the majority of donors. In contrast to the West, female donors had a greater increase in kidney length as compared to their male counterparts in our donor population.

Age at donation could adversely affect renal function paripassu with the physiological changes in the kidney. Donors above 50 years of age were reported to have a higher mean serum Creatinine (p>0.05) in a study. Effect of donor age on prevalence of hypertension and proteinuria are conflicting with few studies showing significantly increased prevalence in donors > 55 years while other study by Bock et al showing no such effect. Mean donor age in our study was 41.26 years as compared to the other studies. Since majority of the donors were in 35-45 years age group and we could not determine any significant effect of age on donor renal function.

**Renal functions**

A) **Proteinuria:** Proteinuria is traditionally reported as a marker of renal damage with few studies demonstrating microalbuminuria as an early predictor of subclinical renal injury. There are conflicting reports on the prevalence of proteinuria in donors with some studies reporting an increase in proteinuria, both overt and microalbuminuria, significantly higher UAE among donors compared to matched controls (UAE 5.4 v/s 3.3 mg/min p<0.05). In contrast, negligible proteinuria of unknown clinical significance was reported with no long term adverse effects on renal disease progression. Although 24% of donors (7/29) developed positive testing for MAU reflecting subclinical hyperfiltration damage Eberhard et al failed to demonstrate clinically relevant function loss in the remaining kidney, 19.8 years after donor nephrectomy. In a meta-analysis of 3100 donors and 1700 controls proteinuria was no different from that observed in controls at 20 years follow up. A few studies have reported increased prevalence of proteinuria with increasing donor age and the time elapsed since nephrectomy. In our study none had overt proteinuria prior to nephrectomy and 14% donors developed overt proteinuria post nephrectomy. 21.3% of donors with hypertension had proteinuria in contrast to 7.4% without hypertension. MAU was positive in 40% after donation. The clinical significance of MAU and proteinuria need to be evaluated in further follow up.

B) **Hypertension:** Donor nephrectomy is associated with hyperfiltration in the remnant kidney and one of the markers of hyperfiltration damage is systemic hypertension. It is logical to presume that donors may have a slight rise in BP post nephrectomy. On the other hand it is an established fact that the kidney has an enormous functional reserve and loss of upto 50% nephron mass does not have any ill effects. The studies on post nephrectomy increase in blood pressure have also not shown consistent results. In a meta-analysis by Kasike et al there was no increase in BP in 3100 nephrectomised patients. In a study from Mayo clinic 24 mildly hypertensive donors had no adverse effects on BP at 1 year of donation. In contrast, Eberhard et al in a study of 29 donors found Hypertension in 29% at 11.13 ± 8 years of follow up. Similarly in another study the prevalence of hypertension in donors was significantly increased. In our study, 46% of donors developed hypertension postnephrectomy.

C) **Glomerular filtration rate:** It is well established that reduced renal mass is a risk factor for hyperfiltration and resultant loss of renal function in the remnant kidney. A meta-analysis by Kasike et al showed
a decline of GFR by 17 ml/min immediately post nephrectomy. This was followed by stabilization of GFR with subsequent rise by 1.4 ml/min/decade. In a recent study from Frankfurt GFR was 101 ± 24 ml/min before nephrectomy and declined to 74 ± 19 ml/min at 11 years. Similarly a decrease in GFR of 30 ml/min was reported in a study in both normotensive as well as hypertensive donors2. Lennerling et al concluded that kidney donation is unsafe with pre nephrectomy GFR of <80 ml/min.19 The mean increase in creatinine as reported in most studies is 0.3 ± 0.1 mg/dl which is not significant. The risk of renal failure in donors is negligible and is reported as 0.2-0.5%.20 In our study we found a fall in GFR by 28 ml/min at a mean duration of 5 years post nephrectomy and no significant change in serum creatinine.

Quality of life: Although the studies are equivocal as regards renal functions, all show an overwhelming positive psychosocial response to kidney donation. In a Norwegian study of 1800 kidney donors, the donors were shown to have a better QOL and lesser mortality than controls due to positive selection during screening.20 Less than 1% of donors regretted donation. Sixty one out of 67 donors were back to work in 6 weeks.18 Indian donors had a similar psychosocial response and were rehabilitated very early.

Co-morbidities: Most studies have focused on hyperfiltration damage. Little attention has been paid to the occurrence of co-morbid conditions not directly related to nephrectomy. In our study, one donor developed diabetes and one had hypothyroidism.

Mortality: Loss of life directly related to kidney donation is rare and is related to immediate post-op surgical and medical complications. In fact, an increased survival may not be surprising as the donors are positively selected and screened for disease. Convincing data on long term mortality were first presented by Ferhman et al in 1997 in which the ratio of observed to expected mortality was 0.76 as compared to a background population.18 In our donor population there were no deaths related to nephrectomy.

Conclusions

Several studies have shown that nephrectomy does not lead to any adverse effects on BP, proteinuria and GFR. But there remain several unanswered questions. Has the follow up been long enough? Does proteinuria herald renal disease? Is kidney donation justified in cases of diseases with a known familial predisposition? Do Indian donors behave differently? This pilot study shows that Indian kidney donors do not behave any differently from their Western counterparts. Although they show significant increase in proteinuria, microalbuminuria, renal size and blood pressure and a decline of GFR after donation, the clinical significance of these changes need to be validated in comparison to population and sibling controls. The follow up irrefutably needs to be longer, on a larger number of donors to draw logical conclusions. The kidney donation programme started in India in 1972. Considering an average of 5000 transplants per year and a lakh strong donor pool, what has been the fate of these donors? Shouldn’t they be followed up? There is an imminent need for a donor registry as has been done in Scandinavia, if we have to fulfill our commitment of 100% safety to donors even long term.

References