Risk of cardiovascular disease in kidney donors as a chronic kidney disease cohort

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Abstract. Kidney donors are a chronic kidney disease (CKD) cohort virtually guaranteed to have a low risk of CKD progression, as they are screened for CKD risk factors beforehand. However, there has been no evidence of cardiovascular disease (CVD), which is an outcome of CKD, for these donors. In this study, the conditions of CKD in kidney donors were investigated and the risk of CVD was estimated using nephrectomy patients, who are thought to have a crude risk of CKD progression, as a model. In 86 kidney donors, estimated glomerular filtration rates (eGFR) were measured, and they were classified according to the CKD stage. Plasma brain natriuretic peptide (BNP) concentrations and urinary albumin (mg/g Cre) levels were also measured as markers for cardiovascular evaluation. A total of 200 nephrectomy patients were similarly classified according to the CKD stage. A multivariate regression analysis was carried out to evaluate the risk factors of CVD. Among the kidney donors, 4.9% were CKD stage 1, 24.6% stage 2 and 70.5% stage 3. Among the nephrectomy patients, 20.5% were CKD stage 2, 66.6% stage 3, 9.5% stage 4 and 3.4% stage 5. Plasma BNP concentrations of the donors were significantly higher compared to those of healthy volunteers (24.5±24.9 vs. 8.6±7.6 pg/ml, p<0.0001). In addition, approximately 16% of the donors had microalbuminuria and 4% had overt proteinuria. The prevalence of new-onset CVD was 2.3% for the donors and 10% for the nephrectomy patients (p=0.0281). By logistic regression analysis of the nephrectomy patients, proteinuria, age and hypertension were significantly independent risk factors for new-onset CVD. Our findings suggest that the risks of CVD may be increased in kidney donors. In our analysis of new-onset CVD in nephrectomy patients, proteinuria, age and hypertension were significantly related factors. This suggests that in the follow-up of kidney donors, those who present these conditions from before or during follow-up should be carefully monitored.

Introduction

According to a previous study, the incidence of end-stage renal disease requiring dialysis in kidney donors 10 or more years after transplantation was less than 0.5% (1). Kidney donors are a chronic kidney disease (CKD) cohort virtually guaranteed a low risk of CKD progression, as they are screened for CKD risk factors beforehand. However, there has been no evidence-based medicine (EBM) on the risk of cardiovascular disease (CVD) for these donors. In this study, the conditions of CKD in kidney donors were investigated and the risk of CVD was estimated using nephrectomy patients, who are thought to have a crude risk of CKD progression, as a model.

Materials and methods

Patients. In 86 kidney donors who were under follow-up as outpatients, estimated glomerular filtration rates (eGFR) were measured, and they were classified according to the CKD stage. Plasma brain natriuretic peptide (BNP) concentrations and single voided fasting urine albumin to creatinine ratios (mg albumin/g creatinine; UACR) were also measured as markers for cardiovascular evaluation. Among the 794 cases of nephrectomy performed at the Osaka City University Hospital since 1978, 200 patients who were under follow-up as outpatients without metastasis or recurrence and without other renal disease, connective tissue disease, infection or malignant disease, were selected and similarly classified according to the CKD stage. Table I shows the patient characteristics of the 89 kidney donors and 200 nephrectomy patients. Informed consent was obtained from all for participation in the study.

Definition of CKD. The eGFR was calculated using the equation of the Japanese Society of Nephrology. The formula was as follows: 194 x (age)^0.287 x (serum creatinine)^1.094, including a correction factor of 0.739 for women (2).

In the kidney donors, proteinuria was defined as a UACR of ≥30 mg/g. Microalbuminuria was defined as a UACR ranging
from 30 to 299 mg/g, and overt proteinuria was defined as a UACR of ≥300 mg/g.

In the nephrectomy patients, proteinuria was defined as a urinary protein level of ≥1+ (≥30 mg/dl) in the dipstick test using a spontaneously and freshly voided urine sample.

We stratified the eGFR into the following ranges: ≥90 ml/min/1.73 m² (stage 1), 60-89 ml/min/1.73 m² (stage 2), 30-59 ml/min/1.73 m² (stage 3), 15-29 ml/min/1.73 m² (stage 4) and <15 ml/min/1.73 m² (stage 5), according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification and staging system. CKD patients were defined as those with kidney damage and kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Risk factors. To evaluate the clinical risk factors, we investigated age, gender, time after operation, the presence or absence of hypertension, diabetes mellitus, dyslipidemia and CVD.

Hypertension was defined by i) the administration of antihypertensive agents and/or a history of this disorder; ii) a systolic blood pressure (SBP) >140 mmHg; or iii) a diastolic blood pressure (DBP) >90 mmHg.

Diabetes mellitus was defined as present when the subject was using oral antidiabetic drugs or insulin, or when fasting blood glucose was ≥126 mg/dl.

Dyslipidemia was defined as present if the subject had total cholesterol >220 mg/dl, triglyceride >150 mg/dl and high-density lipoprotein cholesterol <40 mg/dl, or had received medical treatment for hyperlipidemia.

CVD was defined as angina pectoris, myocardial infarction, stroke, arrhythmia, congestive heart failure, aorta dissection, cerebrovascular disorder or peripheral artery diseases, including arteriosclerosis obliterans.

New-onset CVD was defined as CVD after operation (donated kidney or nephrectomy).

Statistical analysis. Data are presented as a percentage or as the means ± standard deviation (SD) wherever appropriate. The difference between two unpaired groups was analyzed using the Student’s t-test or Mann-Whitney’s U-test. The difference in category data was estimated by the Chi-square test or Fisher’s exact test. For the multivariate analysis of CVD risk factors, logistic regression analysis was performed. In the logistic regression analysis, dummy variables were used for gender and presence or absence of proteinuria, hypertension, diabetes mellitus, dyslipidemia and CVD (1, male; 0, female; 1, presence; 0, absence). Statistical significance was p<0.05. These results were obtained using the Stat View V Statistical System (SAS Institute Inc., Cary, NC, USA).

Results

Comparison of background data between kidney donors and nephrectomy patients. Table I shows the background data of the kidney donors and nephrectomy patients. The mean age of the nephrectomy patients was older than that of the donors (p<0.0001). The female gender was more prevalent in the donors (p<0.0001). The eGFR of the nephrectomy patients was significantly lower than that of the kidney donors (p=0.0007). Hypertension and diabetes mellitus were more prevalent in the nephrectomy patients (p=0.0062 and p<0.0001, respectively). Dyslipidemia was more prevalent in the donors (p=0.0027). The prevalence of CVD was 4.7% for the kidney donors and 16.5% for the nephrectomy patients (p=0.0001). The prevalence of new-onset CVD was 2.3% for the donors and 10% for the nephrectomy patients (p=0.0281). Other clinical variables did not differ significantly.

Prevalence of CKD according to stage in the kidney donors and nephrectomy patients. Among the kidney donors, 4.9% were CKD stage 1, 24.6% stage 2 and 70.5% stage 3 (Fig. 1). Among the nephrectomy patients, 20.5% were CKD stage 2, 66.6% stage 3, 9.5% stage 4 and 3.4% stage 5 (Fig. 2).

Comparison of plasma BNP concentrations between kidney donors and control subjects. Plasma BNP concentrations of the kidney donors were significantly higher than those of the healthy volunteers (24.5±24.9 vs. 8.6±7.6 pg/ml, p<0.0001) (Fig. 3).
Prevalence of albuminuria in the kidney donors. Among the 86 kidney donors, 16% had microalbuminuria and 4% had overt proteinuria (Fig. 4).

Associated factors for new-onset CVD in nephrectomy patients. A univariate logistic regression analysis (Table II) demonstrated that age, proteinuria and hypertension were significant independent risk factors for new-onset CVD. Multivariate regression analysis (Table II) demonstrated that age and proteinuria were significant independent risk factors for new-onset CVD, while hypertension achieved borderline significance.

Discussion

In the present study, the conditions of CKD in kidney donors were investigated and the risk of CVD was estimated using nephrectomy patients, who are thought to have a crude risk of CKD progression, as a model. As a result, among the kidney donors, 4.9% were CKD stage 1, 24.6% stage 2 and 70.5% stage 3. Plasma BNP concentrations of the donors were significantly higher than those of the healthy volunteers. In addition, approximately 16% of the donors had microalbuminuria and 4% had overt proteinuria. These findings suggest that the risks of CVD may be increased in kidney donors. The prevalence of new-onset CVD was 2.3% for the donors and 10% for the nephrectomy patients. Moreover, in our logistic regression analysis of new-onset CVD in nephrectomy patients, proteinuria, age and hypertension were significantly related factors. Our results suggested that in the follow-up of kidney donors, those who present these conditions from before or during follow-up should be carefully monitored.

Currently, there is no clear evidence regarding CVD in kidney donors. Ibrahim et al (3) recently compared the prognosis and risk of end-stage renal disease between 3,698 kidney donors and age, gender, race and BMI-matched controls from the National Health and Nutrition Examination Survey (NHANES) and reported that there was no significant difference. This suggests that the prognosis of donors is about the same as that of the general population. However, such an interpretation should be made with caution, as it is possible that since donors are healthy to begin with, they should live significantly longer lives than the general population. In our study, BNP, which is a marker of cardiac load (4,5), was higher in kidney donors, and the percentage of those with albuminuria,
kidney donors should also be carried out in the future. Yet longitudinal studies investigating CVD risk factors in kidney donor CVD risk using nephrectomy patients as models, are required in the future. Third, the present study evaluated in the nephrectomy patients, long-term longitudinal studies may clarify this point. Second, since there was no relation between new-onset CVD and decreased eGFR in the nephrectomy patients, long-term longitudinal studies are required in the future. Third, the present study evaluated kidney donor CVD risk using nephrectomy patients as models, yet longitudinal studies investigating CVD risk factors in kidney donors should also be carried out in the future.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.09 (1.03-1.16)</td>
<td>0.0031</td>
<td>1.09 (1.02-1.18)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Gender</td>
<td>2.63 (0.74-9.32)</td>
<td>0.1353</td>
<td>2.77 (0.67-11.43)</td>
<td>0.1753</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>0.99 (0.96-1.02)</td>
<td>0.4804</td>
<td>1.03 (0.99-1.07)</td>
<td>0.1574</td>
</tr>
<tr>
<td>Time after operation (years)</td>
<td>1.08 (0.97-1.19)</td>
<td>0.1539</td>
<td>0.99 (0.88-1.11)</td>
<td>0.8679</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.83 (1.41-10.48)</td>
<td>0.0085</td>
<td>2.17 (0.71-6.62)</td>
<td>0.4233</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.50 (0.96-7.02)</td>
<td>0.0616</td>
<td>1.61 (0.50-5.19)</td>
<td>0.4233</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.37 (0.97-6.22)</td>
<td>0.0780</td>
<td>2.73 (0.88-8.49)</td>
<td>0.0821</td>
</tr>
<tr>
<td>Past history of CVD</td>
<td>1.43 (0.30-6.84)</td>
<td>0.6561</td>
<td>0.77 (0.12-5.20)</td>
<td>0.7905</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7.21 (2.72-19.11)</td>
<td>&lt;0.0001</td>
<td>5.87 (1.79-19.29)</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

Significant risk factors of new-onset cardiovascular disease (CVD) were explored among the parameters, including age, gender (1, male; 0, female), hypertension (absent, 0; present, 1), diabetes mellitus (absent, 0; present, 1), dyslipidemia (absent, 0; present, 1), past history of CVD (no, 0; yes, 1) and proteinuria (absent, 0; present, 1).

In conclusion, to label kidney donors as CKD is controversial as there are different opinions on this matter, but it is important in kidney transplantation to clarify the issues that face us now and provide information based on EBM. In the consensus statement of the Amsterdam Forum on the Care of the Live Kidney Donor, the necessity for the long-term follow-up of donors, including their renal function, was called for (13), and it may be appropriate to evaluate their renal and cardiovascular risks by regarding kidney donors as CKD patients. The screening of donors with a past history or risk of CVD should be carried out carefully, and for donors who have already donated their kidney and who have such a history or risk of CVD, an even more strict post-transplant management may be necessary.

Acknowledgements

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References