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.

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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. In 24 age- and gender-matched healthy volunteers (mean age 56.6±11.2 years; 10 males and 14 females), plasma BNP concentrations were measured.

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: $194 \times (\text{age})^{-0.287} \times (\text{serum creatinine})^{-1.094}$, 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

Table I. Comparison of background data between the kidney donors and nephrectomy patients[a].

	Kidney donors (n=86)	Nephrectomy patients (n=200)	p-value[b]
Age (years)	58.7±11.3	67.3±10.2	<0.0001
Gender (males)	34/52	141/59	<0.0001
eGFR (ml/min/1.73 m^2)	55.4±14.5	47.8±15.7	0.0007
Time after operation (years)	6.1±5.8	6.8±4.1	NS
Hypertension (%)	23.2	41.0	0.0062
Diabetes mellitus (%)	2.3	19.0	0.0004
Dyslipidemia (%)	41.8	23.5	0.0027
Proteinuria (%)	20.0	21.5	NS
CVD (%)	4.7	16.5	0.0109
New onset CVD (%)	2.3	10.0	0.0281

[a]Plus-minus values are the means ± SD; [b]kidney donors vs. nephrectomy patients. NS, not significant. CVD, cardiovascular disease.

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 m^2 (stage 1), 60-89 ml/min/1.73 m^2 (stage 2), 30-59 ml/min/1.73 m^2 (stage 3), 15-29 ml/min/1.73 m^2 (stage 4) and <15 ml/min/1.73 m^2 (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 ($p=0.0281$). 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).

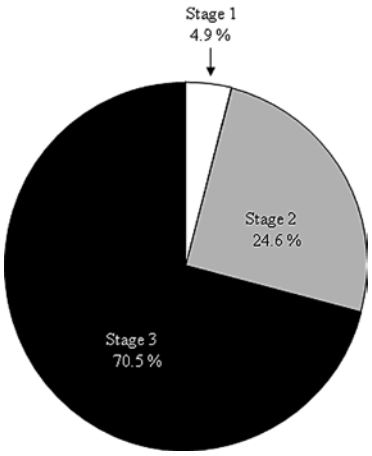

Figure 1. CKD stage of the kidney donors (n=86).

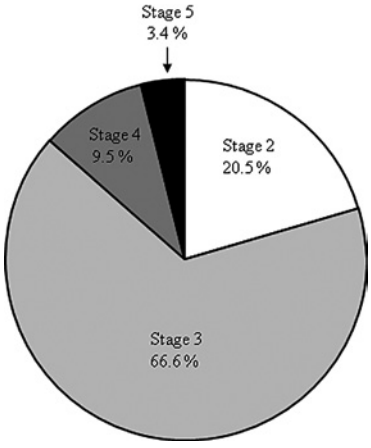

Figure 2. CKD stage of the nephrectomy patients (n=200).

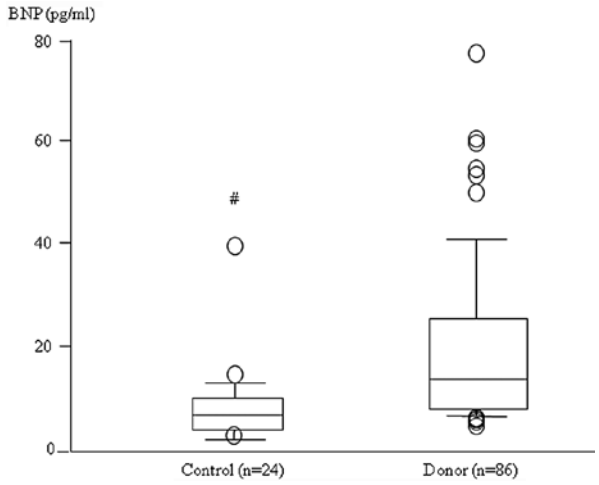

Figure 3. Plasma BNP concentrations of the kidney donors and controls. Box of whisker plots indicate the 10th, 25th, 50th (median), 75th and 90th percentiles of plasma BNP concentrations. #p<0.0001.

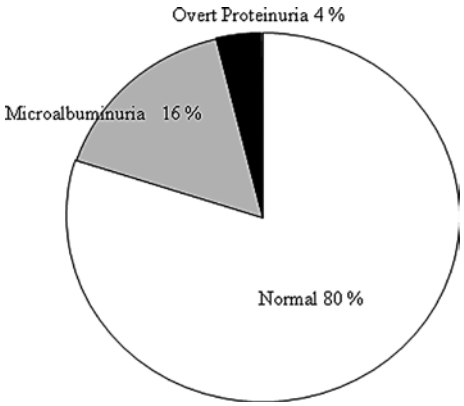

Figure 4. Prevalence of albuminuria in the kidney donors.

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,

Table II. Logistic regression analysis for risk factors affecting new-onset CVD in nephrectomy patients.

	Univariate		Multivariate	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.09 (1.03-1.16)	0.0031	1.09 (1.02-1.18)	0.0116
Gender	2.63 (0.74-9.32)	0.1353	2.77 (0.67-11.43)	0.1753
eGFR (ml/min/1.73 m^2)	0.99 (0.96-1.02)	0.4804	1.03 (0.99-1.07)	0.1574
Time after operation (years)	1.08 (0.97-1.19)	0.1539	0.99 (0.88-1.11)	0.8679
Hypertension	3.83 (1.41-10.48)	0.0085	2.17 (0.71-6.62)	0.4233
Diabetes mellitus	3.50 (0.96-7.02)	0.0616	1.61 (0.50-5.19)	0.4233
Dyslipidemia	2.37 (0.97-6.22)	0.0780	2.73 (0.88-8.49)	0.0821
Past history of CVD	1.43 (0.30-6.84)	0.6561	0.77 (0.12-5.20)	0.7905
Proteinuria	7.21 (2.72-19.11)	<0.0001	5.87 (1.79-19.29)	0.0035

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).

a CVD marker (6-8), in addition to those with overt proteinuria was as high as 20% (Figs. 3 and 4). These results suggest that the risk of CVD may be increased in kidney donors. Based on recent reports on the prognosis of kidney donors, as well as our results, we may hypothesize that since donors are ititially healthy, even if the incidence of CVD events is somewhat increased, mortality is low; therefore, prognosis does not differ from that of the general population, or that even if the risk of CVD increase, the incidence of CVD events does not significantly increase. In any case, we must establish EBM using a cohort study in the future.

What should we keep in mind at present, when there is no EMB on CVD risks in kidney donors? The answer to this may be found in our findings of the nephrectomy patients. The prevalence of new-onset CVD was significantly higher in the nephrectomy patients compared to the donors (Table I). Unlike kidney donors, nephrectomy patients have various risk factors, such as history of diabetes mellitus, hypertension, proteinuria and CVD (Table I). In our logistic regression analysis of new-onset CVD in nephrectomy patients, proteinuria, age and hypertension were significantly related factors (Table II). Evidently, these are also CVD risk factors in the general population (9-12), but our results suggest that in the follow-up of kidney donors, those who present these conditions from before or during follow-up should be carefully monitored. In particular, since the intervention of risk factors, such as proteinuria and hypertension, can be carried out, dietary guidance, lifestyle modification and aggressive treatment using RAS inhibitors may be required.

This study has several limitations. First, because of the cross-sectional design, the results did not indicate causality, but 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.

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

1. Fehrman-Ekholm I, Norden G, Lennerling A, *et al*: Incidence of end-stage renal disease among live kidney donors. Transplantation 82: 1646-1648, 2006.
2. Matsuo S, Imai E, Horio M, *et al*: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992, 2009.
3. Ibrahim HN, Foley R, Tan L, *et al*: Long-term consequences of kidney donation. N Engl J Med 360: 459-469, 2009.
4. Isaac DL: Biomarkers in heart failure management. Curr Opin Cardiol 23: 127-133, 2008.
5. Kalsmith BM: Role of the brain natriuretic peptide in heart failure management. Circ Heart Fail 2: 379, 2009.
6. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39: S1-S266, 2002.
7. Sarnak MJ, Levey AS, Schoolwerth AC, *et al*: Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108: 2154-2169, 2003.

8. Weir MR: Microalbuminuria and cardiovascular disease. Clin J Am Soc Nephrol 2: 581-590, 2007.
9. Hwang SJ, Lin MY, Chen HC, *et al*: Increased risk of mortality in the elderly population with late-stage chronic kidney disease: a cohort study in Taiwan. Nephrol Dial Transplant 23: 3192-3198, 2008.
10. O'Hare AM, Choi AI, Bertenthal D, *et al*: Age affects outcomes in chronic kidney disease. J Am Soc Nephrol 18: 2758-2765, 2007.
11. Shulman NB, Ford CE, Hall WD, *et al*: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. Hypertension 13: I80-I93, 1989.
12. Walker WG, Neaton JD, Cutler JA, Neuwirth R and Cohen JD: Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. Racial and treatment effects. The MRFIT Research Group. JAMA 268: 3085-3091, 1992.
13. The consensus statement of the Amsterdam Forum on the Care of the Live Kidney Donor. Transplantation 78: 491-492, 2004.