Cardiovascular-Renal Changes After Kidney Donation: One-year Follow-up Study

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Background. Long-term consequences of kidney donation are not well known. Most of the studies published were focused on renal risk. In this prospective study, we investigated the changes in cardiovascular function after kidney donation. **Methods.** Thirty-eight living kidney donors were included. In addition to 24-hr ambulatory blood pressure monitoring, serum interleukin-6, vascular cell adhesion molecule (VCAM), and asymmetric dimethylarginine levels were measured. Endothelial function was examined by measuring ischemia-induced flow-mediated dilation (FMD) of the brachial artery. All studies were repeated at 3 months and 12 months after kidney donation. **Results.** The mean serum interleukin-6 levels, both at 3 months and 12 months, were significantly increased as compared to the baseline ($P = 0.007$ and $P < 0.001$, respectively). The mean serum asymmetric dimethylarginine ($P < 0.001$) and VCAM levels ($P < 0.001$) at 12 months were significantly increased as compared to baseline. FMD values at 1 year (9.3% ± 7.1%) were significantly decreased as compared to 3 months (13.0% ± 6.0%, $P = 0.001$) and baseline (13.9% ± 6.3%, $P = 0.002$). In multivariate analysis, serum uric acid ($P = 0.001$), estimated glomerular filtration rate ($P = 0.027$), and VCAM ($P = 0.014$) levels were the independent predictors of FMD 12 months after kidney donation. **Conclusion.** Our findings suggest that kidney donation might increase the cardiovascular risk in kidney donors.

(*Transplantation* 2015;99: 760–764)

Renal transplantation from living donors is still widely practiced in nations with problems in procuring kidneys from deceased donors. Kidney donors might have different types of risks during their lifetime, though majority of previous studies have been mostly focused on possible renal risks.[1,2] Reduced renal mass had previously been implicated in the development of hypertension and in progression of renal insufficiency.[1,3-5] Acute 50% reduction in nephron mass after donation may have adverse effects on vascular health.

Received 31 March 2014. Revision requested 29 April 2014.

Accepted 11 July 2014.

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The authors declare no funding or conflicts of interest.

B.A.Y. participated in the performance of the research and writing of the article. Y.C. participated in the data analysis and writing of the article. A.Y. participated in the performance of the research and writing of the article. A.O. participated in the writing of the article. A.K.B., G.D., and M.S. participated in the performance of the research. A.Y. participated in the research design, performance of the research, and writing of the article.

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ISSN: 0041-13379904-760

DOI: 10.1097/TP.0000000000000414

Interleukin-6 (IL-6), asymmetric dimethyl-arginine (ADMA), vascular cell adhesion molecule-1 (VCAM-1) and uric acid are all known to be associated with endothelial dysfunction and atherosclerotic diseases. Interleukin-6 is an important pro-inflammatory cytokine that plays a significant role in local inflammatory response within atherosclerotic lesions.[6,7] Asymmetric dimethyl-arginine has also been found to be associated with IL-6.[8] Vascular cell adhesion molecule-1 is known as a marker of endothelial activation and has been found to be a predictor of cardiovascular events.[9] We measured all these biomarkers for the assessment of vascular function. In this prospective observational study, we aimed to investigate the changes in vascular function after donation in kidney donors.

RESULTS

The mean age of the cohort was 46 ± 10 (range, 24–65) years. The number of former or current smokers was 8 (21.1%). None of the donors were hypertensive at baseline evaluation. The mean body mass index (BMI) values of the donors at baseline, 3 months, and 1 year were not different (27.21 ± 4.18 kg/m^2, 27.14 ± 3.78 kg/m^2, 27.17 ± 3.70 kg/m^2, respectively, $P = 0.383$).

The laboratory parameters of the patients at baseline, at 3 months and at 1 year, are shown in Table 1. The mean serum creatinine (1.12 ± 0.25 mg/dL, $P < 0.001$), cystatin C (0.95±0.21 mg/L, $P < 0.001$), and uric acid (4.63 ± 1.11 mg/dL, $P < 0.001$) levels at 1 year after donation were significantly increased as compared to baseline (0.80±0.13 mg/dL, 0.71 ± 0.28 mg/L, and 4.05 ± 1.09, respectively). At 1 year, estimated glomerular filtration rate (eGFR) levels by Chronic Kidney Disease Epidemiology Collaboration formula

TABLE 1.

Laboratory findings of donors at baseline, 3 mo, and 1 yr (mean±SD) after donation

	Laboratory data	Baseline	3 mo	1 yr	*P*
Serum	Glucose, mg/dL	89 ± 7	88 ± 11	85 ± 11	0.025
	Creatinine, mg/dL	0.80 ± 0.13	1.12 ± 0.24	1.12 ± 0.25	<0.001
	Cystatine C, mg/L	0.71 ± 0.28	0.92 ± 0.28	0.95 ± 0.21	<0.001
	Uric acid, mg/dL	4.05 ± 1.09	4.78 ± 1.43	4.63 ± 1.11	<0.001
	Calcium, mg/dL	9.41 ± 0.41	9.32 ± 0.34	9.41 ± 0.41	0.895
	Phosphorus, mg/dL	3.27 ± 0.48	3.21 ± 0.52	3.20 ± 0.38	0.414
	Albumin, g/dL	4.18 ± 0.36	4.23 ± 0.40	4.27 ± 0.36	0.759
	Triglyceride, mg/dL	130 ± 69	138 ± 62	145 ± 84	0.096
	Total cholesterol, mg/dL	193 ± 38	201 ± 36	190 ± 33	0.496
	LDL-cholesterol, mg/dL	124 ± 30	124 ± 31	116 ± 27	0.022
	HDL-cholesterol, mg/dL	46 ± 11	46 ± 11	45 ± 12	0.740
	hs-CRP, mg/L	4.02 ± 5.71	4.16 ± 4.31	3.72 ± 4.39	0.736
Hemoglobin, g/dL		13.3 ± 1.5	12.9 ± 1.3	13.1 ± 1.4	0.027
eGFR CKD-EPI, mL/min/1.73 m^2		100 ± 14	70 ± 14	71 ± 16	<0.001
Urinary PCR, mg/mg		115 ± 52	116 ± 43	119 ± 53	0.948
Serum ADMA, µmol/L		0.60 ± 0.36	1.04 ± 0.66	1.92 ± 1.48	<0.001
Serum IL-6, pg/mL		3.73 ± 2.57	5.85 ± 3.77	12.44 ± 9.16	<0.001
Serum VCAM, µg/mL		680 ± 136	733 ± 204	961 ± 334	<0.001
FMD, %		13.9 ± 6.3	13.0 ± 6.0	9.3 ± 7.1	0.001

BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high sensitive C-reactive protein; ADMA, asymmetric dimethylarginine; IL-6, interleukin-6; VCAM, vascular cell adhesion molecule; PCR, protein/creatinine ratio; FMD, flow-mediated dilatation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

(71 ± 16 mL/min/1.73 m^2, $P < 0.001$) were significantly decreased as compared to baseline (100 ± 14 mL/min/1.73 m^2). The mean serum IL-6 levels at 3 months (5.85 ± 3.77 pg/mL) and 1 year (12.44 ± 9.16 pg/mL) were significantly increased as compared to baseline (3.73 ± 2.57 pg/mL) ($P = 0.007$ and $P < 0.001$, respectively). The differences in mean levels of serum creatinine, cystatin C, uric acid, eGFR, and IL-6 levels became significant at 3 months after donation and persisted at 1 year of follow-up (Table 1).

During the follow-up period, there were no differences in mean serum calcium, phosphorus, albumin, triglyceride, total cholesterol, high-density lipoprotein (HDL)-cholesterol, high-sensitive C-reactive protein (hs-CRP), and albuminuria levels (Table 1).

Regarding the assessment of endothelial function, the mean flow-mediated dilation (FMD) values of donors at 1 year (9.3% ± 7.1%) were significantly decreased as compared to 3 months (13.0% ± 6.0%, $P = 0.001$) and baseline (13.9% ± 6.3%, $P = 0.002$). However, there were no significant differences regarding the FMD values between baseline and 3 months after donation ($P = 0.492$) (Figure 1).

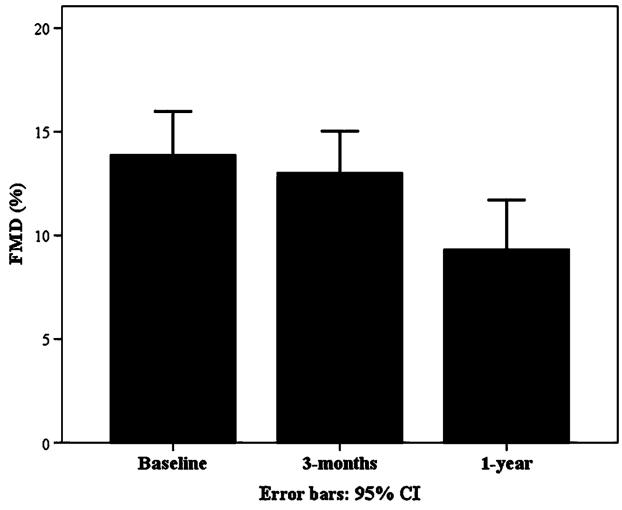

FIGURE 1. Changes in endothelial function after kidney donation.

The mean serum ADMA (1.92 ± 1.48 µmol/L, $P < 0.001$) and VCAM levels (961 ± 334 µg/mL, $P < 0.001$) at 1 year were significantly increased as compared to baseline (0.60 ± 0.36 µmol/L and 680 ± 136 µg/mL, respectively). Increases in ADMA and VCAM levels were also statistically significant at 3 months (1.04 ± 0.66 µmol/L [$P = 0.001$] and 733 ± 204 µg/mL [$P < 0.001$], respectively) compared to baseline levels (Table 1).

We also measured ambulatory blood pressures (ABPs) of the donors at baseline, 3 months, and 12 months after donation. The mean ambulatory systolic and diastolic BP of the donors at baseline at 3 months and at 1 year were not different (118 ± 10 and 74 ± 7 mm Hg, 123 ± 12 and 74 ± 14 mm Hg, 121 ± 11 and 75 ± 8 mm Hg, respectively) (Table 2). None of the patients received antihypertensive treatment during the study.

TABLE 2.

Twenty-four-hour ambulatory blood pressure monitoring at baseline, 3 mo, and 1 yr (mean ± SD) after donation

	Baseline	3 mo	1 yr	*P*
Mean systolic BP, mm Hg	118 ± 10	123 ± 12	121 ± 11	0.137
Mean diastolic BP, mm Hg	74 ± 7	74 ± 14	75 ± 8	0.779
Daytime BP				
Mean systolic BP, mm Hg	123 ± 11	127 ± 13	128 ± 14	0.248
Mean diastolic BP, mm Hg	77 ± 8	79 ± 10	79 ± 10	0.413
Nighttime BP				
Mean systolic BP, mm Hg	110 ± 13	113 ± 18	114 ± 15	0.477
Mean diastolic BP, mm Hg	69 ± 12	69 ± 12	71 ± 12	0.564

BP, blood pressure.

Determinants of Endothelial Dysfunction

The correlation analyses between FMD and laboratory variables at all study points revealed that FMD values at baseline, at 3 months and 1 year, were significantly correlated with serum uric acid levels at baseline (r = –0.336, $P = 0.039$), 3 months (r = –0.344, $P = 0.034$) and at 1 year (r = –0.501, $P = 0.002$), respectively Figure 2A–C). There were no correlations between FMD and other variables including age, BMI, hemoglobin, glucose, creatinine, cystatin C, eGFR, albuminuria, cholesterol, ADMA, IL-6, and VCAM levels at baseline and 3-month study points.

The correlation analyses between ADMA and other laboratory variables at 1 year revealed that serum ADMA level was significantly correlated with serum uric acid (r = –0.501, $P = 0.002$), cystatin C (r = 0.398, $P = 0.015$), eGFR (r = –0.326, $P = 0.049$) and hs-CRP (r = 0.339, $P = 0.040$) levels but not correlated with age, BMI, hemoglobin, serum glucose, creatinine, IL-6, and albuminuria levels.

At the 1-year follow-up, FMD values were significantly correlated with serum levels of cystatin C (r = –0.350, $P = 0.034$), VCAM (r = –0.419, $P = 0.011$) but not correlated with age, BMI, hemoglobin, serum glucose, creatinine, eGFR, albuminuria, and ADMA levels. Although not reaching statistical significance, FMD values tended to be correlated with serum hs-CRP levels (r = –0.306, $P = 0.066$). In multivariate analysis, adjusted for age, BMI, eGFR, serum cystatin C, uric acid, ADMA, VCAM, and IL-6 levels, serum uric acid ($\beta = -0.672$, $P = 0.001$), eGFR ($\beta = -0.442$, $P = 0.027$), and VCAM ($\beta = -0.454$, $P = 0.014$) levels were independent predictors of FMD at 1 year after donation.

DISCUSSION

In this observational study, we found that decrease in nephron mass was associated with the deterioration of endothelial function and increased inflammatory markers closely related to cardiovascular health, such as ADMA and uric acid. Low nephron number, acquired in utero, has been reported to be a risk factor for development of hypertension and renal disease.[10] Patients with primary hypertension were also found to have significantly fewer glomeruli per kidney than matched normotensive controls.[11-13] In our study, although blood pressure did not significantly change after donation, we demonstrated that acquired reduction in nephron mass after donor nephrectomy might adversely affect the cardiovascular health of the donor. These findings are consistent with the hypothesis of "low nephron number." Interestingly, these changes occurred parallel to the decreases in GFR, but without any increase in albuminuria.

Kidney donors provide an ideal opportunity to study the cardiovascular-renal effects of reduced renal mass. In the present study, endothelial function of kidney donors progressively worsened over time, as shown by impaired FMD and increased ADMA levels after kidney donation. To our knowledge, this is the first study which reports the changes in endothelial function after kidney donation.

Endothelial dysfunction (ED) is reported to be the first step in the subsequent development of atherosclerosis. Cardiovascular risk factors identified in the general population, such as hyperlipidemia, hypertension, diabetes mellitus, tobacco use, obesity and inflammation, also contribute to the ED.[14-16] In our study, none of the participants experienced hypertension at the time of donation. Systolic and diastolic BP levels, tobacco use, BMI, serum glucose, and hs-CRP levels were similar at baseline, 3 months, and 12 months after donation. Neither donor age at the time of surgery nor predonation BP were found to be associated with ED after donation. However, serum uric acid levels were significantly increased 3 months after donation and persisted 12 months after donation. These findings are consistent with the recently published study by Kasiske and colleagues.[2] Association of hyperuricemia with ED has also been previously reported in both nonuremic ([17] and uremic populations[18,19] similar to our findings.

Endothelial dysfunction is associated with increased inflammatory activity in nonuremic and uremic patients as previously assessed by the measurement of several biochemical markers, such as IL-6, hs-CRP, ADMA, and VCAM.[8,20-22] In the present study, serum ADMA, IL-6, and VCAM levels were progressively increased after kidney donation similar to the study by Kielstein and colleagues.[22] In this particular study, despite a temporary decline in serum ADMA levels during the first 24 hr after kidney donation, ADMA levels were elevated above baseline after the first week of kidney donation. In the study by Ravani et al.,[23] ADMA has been shown to be significantly inversely correlated with eGFR. Indeed, higher levels of ADMA might be the result of decreased GFR; however, this does not necessarily mean that increased ADMA in this situation has no pathophysiologic implication in endothelial dysfunction. Currently, it is not very well known that increased ADMA in case of decreased GFR is a

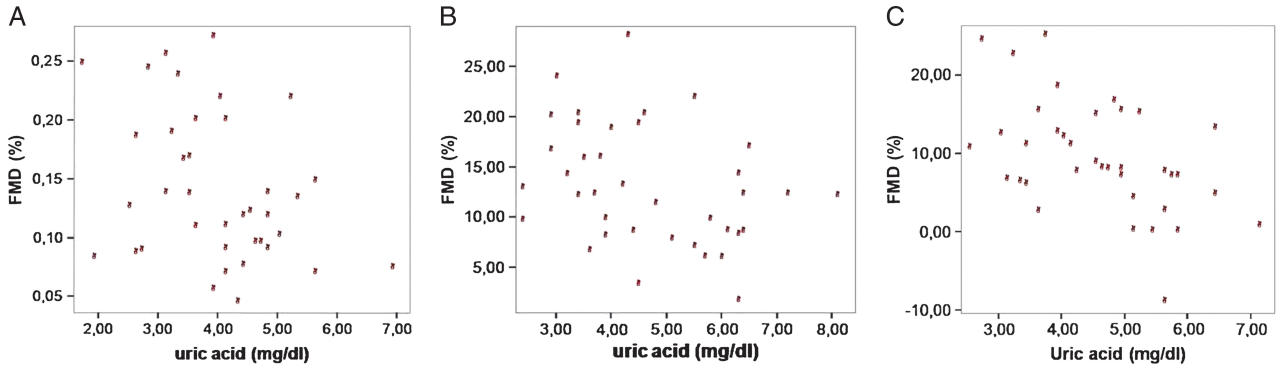

FIGURE 2. Correlations between serum uric acid and FMD at baseline (A), 3 months after donation (B), and 12 months after donation (C). FMD, flow-mediated dilation.

consequence of decreased elimination of ADMA or increased production.

In our study, inflammation is increased after donation, which was associated with ED. In addition to uric acid, increased inflammation may also play a role in the deterioration of endothelial function after kidney donation.

A reduction in nephron number, in the absence of compensatory hyperfunction, would be expected to result in a lower total GFR and creatinine clearance. A low nephron number is a recently identified cause of arterial hypertension, cardiorenal damage, and left ventricular dysfunction.[24,25] Serum cystatin C has gained recognition as an endogenous marker of kidney function. In our study, progressive increase in cystatin C levels was observed after donation. This increase in cystatin C levels was correlated with ADMA and ED. Serum cystatin C levels were also detected as one of the independent predictors of FMD levels at 1 year.

Although an increased risk of hypertension and proteinuria were found in long-term follow-up of kidney donors over 10 years,[26] a recent study by Kasiske and colleagues[2] reported a slight decline in systolic BP levels between baseline and 6 months. In the present study, we have measured ABPs of all kidney donors. Although the difference did not reach statistical significance, slight increases in mean ambulatory systolic and diastolic BP levels, both in day and night time, were observed 3 months after donation, which persisted at 1 year of follow up. Registry studies were unable to determine whether mild renal dysfunction after kidney donation subsequently led to the development of cardiovascular disease over a 2-year period.[27] These findings suggested that ED might develop earlier than increase in blood pressure after kidney donation.

In conclusion, our study demonstrated that reduced nephron mass because of kidney donation is associated with progressive deterioration of endothelial function along with decreased GFR, increased serum uric acid levels, and markers of inflammation. Our findings suggest that kidney donation might increase the risk of cardiovascular diseases in kidney donors. Long-term prospective studies are needed to further demonstrate the cardiovascular complications of kidney donation.

MATERIALS AND METHODS

Patients

In this study, 38 (13 men, 25 women) living kidney donors between the ages of 18 and 70 were included for the assessment of cardiovascular and renal functions. A review of medical records including information on demographic features; BMI; risk factors for cardiovascular diseases; thyroid, cardiac, and liver function tests were obtained. Amsterdam forum criteria were considered for eligibility of kidney donation.[28] None of the donors had low (<80 mL/min/1.73 m^2) creatinine clearance, diabetes mellitus, hypertension, valvular heart disease, previous coronary intervention, congestive heart failure (New York Heart Association class II or greater), cardiac arrhythmia, a history of cerebral infarction or transient ischemic attack, and active infection or noninfectious overt inflammation. The subjects who were on antihypertensive treatment before the enrollment were excluded from the study.

Our examinations of the patients conformed to good medical and laboratory practices and the recommendations of the Declaration of Helsinki on Biomedical Research involving Human Subjects. This study was approved by Ethical Committee of Istanbul School of Medicine. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism." This study is registered with ClinicalTrials.gov, number NCT01564966.

Study Design

Markers of endothelial function and measurements of biochemical variables at baseline before nephrectomy (–2 preoperative day) and on the 3rd and 12th months after donor nephrectomy were obtained. All study participants completed the 12-month study follow-up.

Clinical and Laboratory Assessments

We obtained the medical history, demographic features, laboratory tests, and physical examinations from all donors. The ABP monitoring was performed in all patients over a 24-hr period by the oscillometric method using a fully automatic noninvasive recorder (Spacelabs 90207; Redmond, WA). Donors showing a nocturnal fall of less than 10% in systolic BP were considered as nondippers.[29,30] Hypertension was defined as a systolic BP of 140 mm Hg or higher, a diastolic BP of 90 mm Hg or higher, or a known diagnosis of hypertension.

Blood samples were taken before nephrectomy (–2 preoperative day) and 3 months and 12 months after the nephrectomy for measurements of hemoglobin, glucose, cystatin C, creatinine, electrolytes, uric acid, calcium, phosphorus, albumin, triglycerides, total cholesterol, and LDL and HDL cholesterol levels. The Chronic Kidney Disease Epidemiology Collaboration formula was used to estimate eGFR preoperatively as well as after the nephrectomy.[31] Serum total cholesterol was considered abnormal when values were higher than 200 mg/dL. Serum HDL levels were considered abnormal when values were less than 40 mg/dL in men and less than 50 mg/dL in women.[32] Serum IL-6 (Biosource, CA), VCAM (Biosource) and ADMA (Biovendor, Brno, Czech Republic) concentrations were also determined before the nephrectomy (–2 preoperative day) and after the nephrectomy using the commercially available enzyme-linked immunosorbent assay.

Endothelial Function Measurements

The FMD of the brachial artery after transient ischemia, which is a noninvasive method for assessing endothelial function was done according to the method defined by Celermajer et al.[33] using high-resolution ultrasound machine (10 MHz transducer, attached to a standard Vingmed System Five, Norway). The FMD was expressed as the percentage change in the brachial artery diameter from baseline to after reactive hyperemia. All measurements were performed by a single investigator blinded to clinical details and brachial artery measurements of the study participants.

Statistical Analyses

Statistical comparisons of individual groups were based on Student *t* test for continuous variables and on Fisher exact test for discrete variables. Parametric and nonparametric

tests were used according to the distribution pattern of the data of each variable. Associations between groups and dichotomous variables were examined by using the chi-square test or Fisher exact test where appropriate. The relations between various parameters with normal distribution were assessed using Pearson correlation coefficient. Correlations between numerical parameters with non-normal distribution were analyzed with Spearman ρ correlation test. Multiple linear regression analysis was applied to identify independent determinants of outcome variables after adjustment for potential confounding factors affecting outcome variables. The statistical analysis was carried out by Statistical Package for Social Sciences for Windows ver. 15.0 (SPSS Inc., Chicago, IL). Data were expressed as mean±SE, with significance level of P less than 0.05. For multiple comparisons, Bonferroni correction was done, and P less than 0.0125 (0.05/3) was accepted as significant.

ACKNOWLEDGMENTS

The authors thank Simin Goral, MD (Renal Electrolyte and Hypertension Division, University of Pennsylvania) for her critical review and editing of the article. The authors also thank to Sevda Ozel, MD (Department of Biostatistics, Istanbul Faculty of Medicine) for her help in the statistical analysis of the data.

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