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Original Investigation

A Prospective Controlled Study of Living Kidney Donors: Three-Year Follow-up

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Background: There have been few prospective controlled studies of kidney donors. Understanding the pathophysiologic effects of kidney donation is important for judging donor safety and improving our understanding of the consequences of reduced kidney function in chronic kidney disease.

Study Design: Prospective, controlled, observational cohort study.

Setting & Participants: 3-year follow-up of kidney donors and paired controls suitable for donation at their donor's center.

Predictor: Kidney donation.

Outcomes: Medical history, vital signs, glomerular filtration rate, and other measurements at 6, 12, 24, and 36 months after donation.

Results: At 36 months, 182 of 203 (89.7%) original donors and 173 of 201 (86.1%) original controls continue to participate in follow-up visits. The linear slope of the glomerular filtration rate measured by plasma iohexol clearance declined 0.36 ± 7.55 mL/min per year in 194 controls, but increased 1.47 ± 5.02 mL/min per year in 198 donors ($P = 0.005$) between 6 and 36 months. Blood pressure was not different between donors and controls at any visit, and at 36 months, all 24-hour ambulatory blood pressure parameters were similar in 126 controls and 135 donors (mean systolic blood pressure, 120.0 ± 11.2 [SD] vs 120.7 ± 9.7 mm Hg [$P = 0.6$]; mean diastolic blood pressure, 73.4 ± 7.0 vs 74.5 ± 6.5 mm Hg [$P = 0.2$]). Mean arterial pressure nocturnal dipping was manifest in 11.2% ± 6.6% of controls and 11.3% ± 6.1% of donors ($P = 0.9$). Urinary protein-creatinine and albumin-creatinine ratios were not increased in donors compared with controls. From 6 to 36 months postdonation, serum parathyroid hormone, uric acid, homocysteine, and potassium levels were higher, whereas hemoglobin levels were lower, in donors compared with controls.

Limitations: Possible bias resulting from an inability to select controls screened to be as healthy as donors, short follow-up duration, and dropouts.

Conclusions: Kidney donors manifest several of the findings of mild chronic kidney disease. However, at 36 months after donation, kidney function continues to improve in donors, whereas controls have expected age-related declines in function.

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INDEX WORDS: Chronic kidney disease (CKD); renal insufficiency; unilateral nephrectomy; glomerular filtration rate (GFR); kidney function; patient safety; parathyroid hormone (PTH); uric acid; homocysteine; potassium; hemoglobin; mineral and bone disorders; living kidney donation; kidney transplantation; Assessing Long Term Outcomes in Living Kidney Donors (ALTOLD).

Editorial, p. 1

Understanding the pathophysiologic effects of kidney donation is important for both ensuring the safety of donors and determining why mild reductions in kidney function are associated with cardiovascular disease and other adverse outcomes in the general population.[1,2] Studies of kidney donors generally have been of low quality.[3] Most studies have been small, very few have been prospective, and identifying comparable contemporaneous controls

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for donors has been problematic. We reported the immediate short-term effects of kidney donation in a multicenter prospective study in which each living donor enrolled with a comparable healthy control.[4] We now report results of the first 36 months of follow-up.

METHODS

Participant Protections

Informed consent was obtained from each participant. The study was approved by the institutional review board at each participating site (University of Minnesota no. 0503M67993).

Study Design

In this prospective observational cohort study, donors and controls were enrolled before donation. Details of study design and acute changes from predonation to 6 months have been described in detail previously.[4] Briefly, kidney donors were enrolled after acceptance for donation, but before donation had taken place. For every donor who was enrolled, a control also was enrolled at the same site. However, in some cases, donors did not donate and replacements were recruited. The target enrollment was 200 donor and control pairs, or 400 participants. Only donors who donated and completed at least one postdonation follow-up visit were analyzed. Controls were required to meet the same donor eligibility criteria as donors at that site. However, controls did not undergo renal imaging or invasive testing. Donors and controls were scheduled to complete a predonation visit and visits at 6, 12, 24, and 36 months after donation. The laboratory measurements obtained were those reported in the accompanying tables, and details of methods for measurement have been reported previously.[4] We now report visits at 6, 12, 24, and 36 months after donation. None of the data in this report extend beyond 36 months postdonation.

Data Collected

Participants were evaluated in the clinical research center at each participating site. Blood pressure (BP) was measured 3 times at 1-minute intervals after participants were seated and resting for at least 5 minutes using a standard protocol. At 36 months, 24-hour ambulatory BP recordings also were obtained using an automated recording device (Spacelabs Inc). Laboratory tests were performed in a central laboratory as previously described.[4]

An iohexol plasma decay method was used to determine measured glomerular filtration rate (mGFR).[4] GFR was also estimated (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatine equation, a 4-variable formula.[5] In addition, GFR was estimated with the 4-variable CKD-EPI cystatin C equation and the CKD-EPI creatinine–cystatin C equation.[6]

Statistical Analysis

The prespecified primary end point was the difference between donors and controls of the slope of the mGFR between 6 and 36 months after donation. The effect of age on the difference in slope of mGFR between donors and controls was analyzed with a generalized linear mixed-effects model. Multiple secondary end points included eGFR, BP, and laboratory parameters as previously described.[4] Differences between groups and visits were assessed using analysis of variance with repeated measures (generalized linear mixed-effects models). This analysis assessed the independent effects of donors versus controls; visits at 6, 12, 24, and 36 months; and the interaction between these 2 effects. No adjustment was made for multiple comparisons. Results are expressed as mean ± standard deviation unless otherwise indicated and were considered statistically significant for $P < 0.05$. Variables that were not normally distributed were logarithmically transformed for analysis, but results were expressed as median and interquartile range (IQR; not logarithmically transformed). Differences in categorical variables between groups and among visits were assessed with χ^2 test. All analyses were carried out with SAS, version 9.2, for the personal computer (SAS Institute Inc).

RESULTS

Participant Characteristics

At 36 months, 182 of 203 (89.7%) original study donors and 173 of 201 (86.1%) original controls had follow-up visits. Age, sex, race/ethnicity, height, weight, body mass index, hip circumference, and waist circumference were not different between donors and controls (Table S1, available as online supplementary material). The only statistically significant difference in medication use between donors and controls was that nonsteroidal anti-inflammatory drugs were used less commonly in donors than in controls; 2.5% versus 6.6% ($P = 0.05$) at 6 months and 3.0% versus 8.3% ($P = 0.02$) at 12 months in donors and controls respectively (Table S2).

BP and Heart Rate

Both systolic and diastolic BP increased slightly but significantly over time, but there were no differences between donors and controls (Tables 1 and S3). At the 36-month visit, 135 of 182 (74.2%) donors and 126 of 173 (72.8%) controls had 24-hour ambulatory BP measurements (Table 2). There were no statistically significant differences between donors and controls in any of the 24-hour ambulatory BP parameters.

Kidney Function

Both mGFR and eGFR declined in controls between 6 and 36 months, whereas they increased in donors (Table 3). As a result, there was a statistically significant difference between change in kidney function (slopes) between donors and controls (Table 4; Fig 1). The effect of donation on rate of change in mGFR did not differ by age (Table 5). Urine total protein excretion was not different between visits or between donors and controls (Table 3). Urine albumin-creatinine ratio was lower in donors versus controls, but tended to increase in donors, but not controls (Table 3).

Laboratory Parameters

Hemoglobin concentrations were lower in donors compared with controls, but this difference appeared to narrow with duration of follow-up (Table 6). Serum albumin, C-reactive protein (CRP), and fibrinogen concentrations were not different between donors and controls. Homocysteine, uric acid, and serum potassium levels were each persistently higher in donors than controls. Serum phosphorus levels were lower, whereas parathyroid hormone levels were higher and serum calcium levels were not different in donors

Table 1. Heart Rate and BP

Test	Group	Visit (time after donation)				P[a]		
		6 mo	12 mo	24 mo	36 mo	Donors vs Controls[b]	Visit[c]	Interaction[d]
Heart rate (beats/min)	Controls	66.3 ± 10.0 (198)	66.6 ± 10.3 (193)	67.0 ± 9.3 (180)	66.7 ± 9.7 (169)	0.9	0.1	0.7
	Donors	66.3 ± 9.6 (200)	66.6 ± 9.5 (196)	66.9 ± 10.0 (184)	66.6 ± 9.2 (181)			
Systolic BP (mm Hg)	Controls	115.7 ± 12.2 (198)	116.2 ± 11.8 (193)	117.2 ± 13.3 (180)	117.3 ± 12.8 (170)	0.6	<0.001	0.8
	Donors	115.2 ± 11.3 (200)	116.4 ± 12.4 (196)	116.2 ± 11.6 (184)	117.5 ± 12.0 (182)			
Diastolic BP (mm Hg)	Controls	70.0 ± 8.5 (198)	70.1 ± 9.0 (193)	71.0 ± 9.1 (180)	71.6 ± 8.5 (170)	0.7	<0.001	0.8
	Donors	70.4 ± 8.5 (200)	70.3 ± 8.6 (196)	70.7 ± 8.3 (184)	72.1 ± 8.4 (182)			
Pulse pressure (mm Hg)	Controls	45.7 ± 8.8 (198)	46.2 ± 8.4 (193)	46.2 ± 9.7 (180)	45.7 ± 8.7 (170)	0.3	0.9	0.6
	Donors	44.8 ± 8.2 (200)	46.1 ± 8.6 (196)	45.5 ± 8.4 (184)	45.4 ± 8.9 (182)			

Note: Values are given as mean ± standard deviation (number sampled).

Abbreviation: BP, blood pressure.

[a]Analysis of variance with repeated measures. Each variable was analyzed separately and no adjustment was made for multiple comparisons. Values not normally distributed were logarithmically transformed before analysis.

[b]Donors versus controls, *P* values test overall differences between donors and controls.

[c]Visit *P* values test differences among the 4 visits.

[d]Interaction *P* values test the interaction between donors versus controls and between visits.

Table 2. Twenty-Four Hour Ambulatory BP Results at 36 Months

Parameter	Donors (n = 135)	Controls (n = 126)	P[a]
Duration of recording (h)	24.4 ± 11.5	25.1 ± 9.9	0.6
No. of measurements	43.8 ± 15.4	45.4 ± 16.6	0.4
Systolic BP (mm Hg)	120.7 ± 9.7	120.0 ± 11.2	0.6
Diastolic BP (mm Hg)	74.5 ± 6.5	73.4 ± 7.0	0.2
MAP (mm Hg)	89.9 ± 6.8	88.7 ± 7.3	0.2
Pulse pressure (mm Hg)	46.3 ± 7.3	46.7 ± 8.6	0.7
Heart rate (beats/min)	73.5 ± 9.1	71.6 ± 8.8	0.09
Systolic BP dip (%)	9.2 ± 5.4	8.4 ± 6.3	0.3
Diastolic BP dip (%)	13.7 ± 7.3	13.2 ± 7.4	0.6
MAP dip (%)	11.3 ± 6.1	11.2 ± 6.6	0.9
High systolic BP[b] (%)	18.8 ± 21.9	19.8 ± 24.2	0.8
High diastolic BP[c] (%)	22.2 ± 19.4	16.8 ± 19.2	0.07

Note: Values are given as mean ± standard deviation.

Abbreviations: BP, blood pressure; MAP, mean arterial pressure.

[a]A *t* test.

[b]BP > 135 mm Hg daytime or >120 mm Hg night-time.

[c]BP > 85 mm Hg daytime or >80 mm Hg night-time.

compared with controls. Total, low-density lipoprotein, and high-density lipoprotein cholesterol levels all increased slightly over time, but were not different in donors and controls. Triglyceride and lipoprotein(a) levels also were not different between donors and controls. Hemoglobin A_{1c} levels and homeostasis model assessment of insulin resistance (HOMA-IR) all increased slightly but significantly during follow-up in both groups, but none of the measures of glucose homeostasis were different between donors and controls.

DISCUSSION

Few prospective studies of living kidney donors have enrolled contemporaneous controls who are as healthy as donors. In the current study, a control was selected for each donor based on donation eligibility criteria used by the donor's transplantation program. The fact that medication use was similar in donors and controls is reassuring that both groups were equally healthy (Table S2). The lower use of nonsteroidal anti-inflammatory drugs (excluding aspirin) among donors at 6 and 12 months after donation likely reflects admonitions of caregivers to avoid these agents. Most medication use was lower than that reported in the general population. For example, an antihypertensive agent was used in only 5.0% predonation and 7.3% at 36 months, whereas in the general US adult population in 2007 to 2008, a total of 26.1% (95% confidence interval [CI], 24.5%-27.8%) used an antihypertensive agent.[7] Lipid-lowering medications were used by 15.9% (95% CI, 14.6%-17.1%) of US adults,[7] whereas they were used in 7.5% of our participants predonation and in

Table 3. Kidney Function at 6, 12, 24, and 36 Months After Kidney Donation

Test	Group	Visit (time after donation)				*P*[a]		
		6 mo	12 mo	24 mo	36 mo	Donors vs Controls[b]	Visit[c]	Interaction[d]
mGFR (mL/min)	Controls	104.9 ± 20.2 (194)	105.4 ± 20.2 (189)	104.5 ± 19.7 (177)	104.1 ± 20.7 (168)	<0.001	0.04	<0.001
	Donors	74.3 ± 12.9 (193)	74.5 ± 13.3 (192)	76.3 ± 13.9 (182)	77.5 ± 14.0 (180)			
mGFR (mL/min/1.73 m^2)	Controls	94.6 ± 15.1 (194)	94.8 ± 15.3 (189)	94.1 ± 14.9 (177)	93.2 ± 14.6 (168)	<0.001	0.4	<0.001
	Donors	67.6 ± 10.1 (193)	67.5 ± 10.4 (192)	69.4 ± 10.5 (182)	69.7 ± 10.1 (180)			
Scr (mg/dL)	Controls	0.80 ± 0.17 (198)	0.80 ± 0.16 (193)	0.80 ± 0.15 (182)	0.80 ± 0.14 (173)	<0.001	<0.001	<0.001
	Donors	1.16 ± 0.22 (199)	1.15 ± 0.22 (196)	1.12 ± 0.22 (185)	1.10 ± 0.23 (182)			
$eGFR_{cr}$ (mL/min/1.73 m^2)	Controls	99.1 ± 16.0 (198)	98.3 ± 16.7 (193)	97.9 ± 15.2 (182)	97.5 ± 14.6 (173)	<0.001	0.007	<0.001
	Donors	65.5 ± 13.1 (199)	66.5 ± 13.3 (196)	68.0 ± 14.3 (185)	69.3 ± 14.6 (182)			
CysC (mg/dL)	Controls	0.81 ± 0.14 (198)	0.81 ± 0.13 (193)	0.80 ± 0.14 (182)	0.81 ± 0.13 (173)	<0.001	<0.001	0.008
	Donors	1.11 ± 0.17 (199)	1.08 ± 0.15 (196)	1.07 ± 0.15 (185)	1.06 ± 0.16 (182)			
$eGFR_{cys}$ (mL/min/1.73 m^2)	Controls	102.3 ± 17.5 (198)	102.3 ± 15.9 (193)	103.3 ± 17.2 (182)	101.6 ± 16.5 (173)	<0.001	0.02	0.01
	Donors	71.6 ± 15.3 (199)	73.6 ± 14.8 (196)	74.5 ± 15.2 (185)	75.2 ± 16.3 (182)			
$eGFR_{cr\text{-}cys}$ (mL/min/1.73 m^2)	Controls	101.3 ± 16.8 (198)	100.7 ± 15.3 (193)	101.5 ± 16.0 (182)	100.3 ± 15.3 (173)	<0.001	<0.001	<0.001
	Donors	67.4 ± 12.6 (198)	68.8 ± 12.5 (196)	70.1 ± 13.1 (185)	71.2 ± 14.1 (182)			
Urea nitrogen (mg/dL)	Controls	14.5 ± 4.0 (198)	14.5 ± 4.1 (193)	14.6 ± 4.1 (182)	14.5 ± 3.7 (173)	<0.001	0.5	0.7
	Donors	18.0 ± 4.4 (200)	17.5 ± 4.0 (196)	17.7 ± 4.4 (185)	17.7 ± 4.5 (182)			
Urine PCR (g/g)	Controls	62 [50-128] (195)	70 [50-106] (193)	61 [49-100] (178)	63 [47-122] (169)	0.6[e]	0.3[e]	0.7[e]
	Donors	70 [50-116] (201)	70 [50-116] (197)	60 [46-114] (182)	60 [48-111] (181)			
Urine ACR (mg/g)	Controls	4.7 [3.4-7.1] (193)	5.0 [3.5-7.7] (191)	5.1 [3.6-7.2] (178)	4.7 [3.4-7.3] (168)	<0.001[e]	0.002[e]	0.001[e]
	Donors	3.6 [2.4-5.8] (198)	3.5 [2.4-6.1] (195)	3.8 [2.8-6.6] (182)	4.2 [2.7-7.1] (180)			

Note: Values are given as mean ± standard deviation or median [interquartile range] (number sampled). Conversion factors for units: Scr in mg/dL to μmol/L, ×88.4; urea nitrogen in mg/dL to mmol/L, ×0.357.

Abbreviations and definitions: ACR, albumin-creatinine ratio; CysC, cystatin C; $eGFR_{cr}$, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine equation; $eGFR_{cr\text{-}cys}$, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine−cystatin C equation; $eGFR_{cys}$, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration cystatin C equation; mGFR, measured glomerular filtration rate by iohexol plasma clearance; PCR, protein-creatinine ratio; Scr, serum creatinine.

[a]Analysis of variance with repeated measures. Each variable was analyzed separately and no adjustment was made for multiple comparisons. Values not normally distributed were logarithmically transformed before analysis.

[b]Donors versus controls *P* values test overall differences between donors and controls.

[c]Visit *P* values test differences among the 4 visits.

[d]Interaction *P* values test the interaction between donors versus controls and between visits.

[e]Based on logarithmically transformed values.

Table 4. Changes in Kidney Function Over Time

Measurement	Follow-up Duration (mo)	Group	Rate of Change in Kidney Function	P[a]
mGFR (mL/min per y)	12-36	Controls	−0.36 ± 7.55 (194)	0.005
		Donors	1.47 ± 5.02 (198)	
	36	Controls	−0.19 ± 5.31 (172)	0.002
		Donors	1.30 ± 3.49 (181)	
mGFR (mL/min/1.73 m^2 per y)	12-36	Controls	−0.44 ± 7.35 (194)	0.01
		Donors	1.09 ± 4.28 (198)	
	36	Controls	−0.39 ± 4.81 (172)	0.004
		Donors	0.84 ± 3.09 (181)	
$eGFR_{cr}$ (mL/min/1.73 m^2 per y)	12-36	Controls	−1.04 ± 6.16 (196)	<0.001
		Donors	1.82 ± 4.92 (200)	
	36	Controls	−0.46 ± 3.68 (173)	<0.001
		Donors	1.60 ± 3.75 (182)	
$eGFR_{cys}$ (mL/min/1.73 m^2 per y)	12-36	Controls	−0.33 ± 7.36 (196)	0.003
		Donors	1.82 ± 6.76 (200)	
	36	Controls	0.16 ± 4.68 (173)	0.04
		Donors	1.21 ± 5.06 (182)	
$eGFR_{cr\text{-}cys}$ (mL/min/1.73 m^2 per y)	12-36	Controls	−0.73 ± 6.38 (196)	<0.001
		Donors	1.89 ± 4.58 (200)	
	36	Controls	−0.07 ± 3.85 (173)	<0.001
		Donors	1.49 ± 3.81 (182)	

Note: Unless otherwise indicated, changes in kidney function over time (slopes) are given as mean ± standard deviation (number sampled). Shown are slopes with and without dropping cases that did not have a 36-month visit.

Abbreviations and definitions: $eGFR_{cr}$, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine equation; $eGFR_{cr\text{-}cys}$, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine−cystatin C equation; $eGFR_{cys}$, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration cystatin C equation; mGFR, glomerular filtration rate measured by iohexol plasma clearance.

[a]A *t* test.

12.1% at 36 months. Medication for diabetes was used in 7.1% (95% CI, 6.3%-8.0%) of US adults, but in none of the participants in the current study.

A major finding of this study is that change in mGFR over time (slope) after donation was significantly different in donors and controls (Table 4). The gradual increase in mGFR among donors between 6 and 36 months is especially notable. Additional follow-up may help determine how long function will continue to increase. If the increase is due to compensatory hypertrophy, one might expect that the increase would be greater in younger compared with older donors. However, this was not found to be the case, at least during the 3-year follow-up postdonation (Table 5). We searched the literature for studies reporting posttransplantation change in mGFR and could locate only 2 with mGFR measured twice, the second time more than 1 year after donation. Saran et al[8] measured chromium 51–labeled EDTA clearances in 47 donors at 10 and 20 years after donation from a starting cohort of 75 donors. They reported that mGFR increased by a mean of 5.97 ± 17.44 (standard deviation) mL/min/1.73 m^2 (*P* by paired *t* test = 0.03) during this 10-year period. Tent et al[9] compared mGFR (^{125}I-iothalamate) and effective renal plasma flow (^{131}I-hippuran) in 13 hypertensive and 26 normotensive donors at 2 months and 5 years postdonation from a starting cohort of 47 hypertensive and 94 normotensive donors. Changes in mGFR between 2 months and 5 years were not reported, but mGFR appeared to be similar between 2 months and 5 years in an accompanying figure.

In contrast to donors, controls exhibited a gradual decline in mGFR (Table 4). This also is notable because very few studies have examined serial changes in mGFR in healthy individuals. The Baltimore Longitudinal Aging Study often is cited as the definitive study showing that kidney function declines

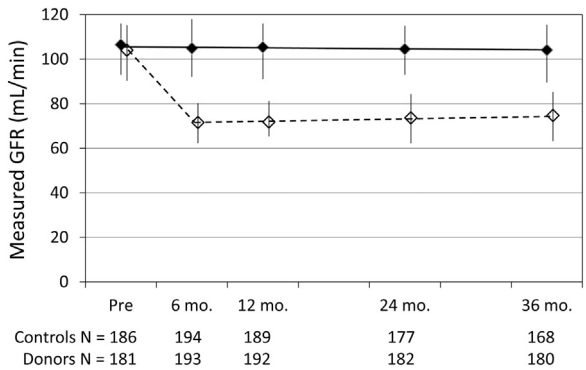

Figure 1. Measured glomerular filtration rate (GFR) in controls (solid line) and donors (dashed line) before and 6, 12, 24, and 36 months after donation. Values are means and interquartile ranges.

Table 5. Lack of Association of Age With Changes in Kidney Function in Donors and Controls

Measurement	Age (y)	Group	Rate of Change in Kidney Function	*P*[a]		
				Donors vs Controls[b]	Younger vs Older[c]	Interaction[d]
mGFR (mL/min per y)	<45	Controls	0.08 ± 9.46 (91)	0.007	0.9	0.2
		Donors	1.02 ± 5.31 (89)			
	≥45	Controls	−0.75 ± 5.34 (103)			
		Donors	1.83 ± 4.77 (109)			

Note: Values are given as mean ± standard deviation (number sampled).
Abbreviation: mGFR, glomerular filtration rate measured by iohexol plasma clearance.
[a]Analysis of variance.
[b]Donors versus controls *P* values test differences between donors and controls.
[c]Younger versus older *P* values test difference in age between younger (<45 years) and older (≥45 years).
[d]Interaction *P* values test differences between donors versus controls and age.

~1 mL/min per year.[10,11] However, that study used men and 24-hour urine creatinine clearances collected prospectively over time. Thus, the current prospective study of healthy men and women with serial measurements of mGFR using iohexol clearance provides an important confirmation of the decline in kidney function with age in apparently healthy individuals.

This study also provides an opportunity to compare different equations and markers of change in eGFR over time compared with change in mGFR (Table 4). Most studies comparing eGFR equations with mGFR have been cross-sectional. The prospective measurement of GFR will help answer the important question of whether changes in eGFR over time accurately reflect changes in mGFR.

Another important finding in this study is the lack of difference in BP between donors and controls for the first 3 years after donation. Previous studies of BP in donors have produced conflicting results (Table S4). A meta-analysis of observational studies published in 2005 included 48 studies of BP in kidney donors.[12] However, few of these studies included controls. In those that did, 10 years after donation, systolic and diastolic BPs were reported to be, respectively, 6 and 4 mm Hg higher in donors than controls. Garg et al,[13] using claims data, reported that the incidence of hypertension was significantly higher in donors than controls at a mean of 6.2 years after donation. They acknowledged that donors may have been followed up more closely than controls, which may have led to hypertension being diagnosed more often. Ibrahim et al[14] retrospectively studied 255 kidney donors matched to 255 controls from the National Health and Nutrition Examination Survey (NHANES). They reported that systolic BP was lower in donors compared with controls, whereas diastolic BP and the incidence of hypertension were not different between the 2 groups. Ethnicity may be an important determinant of the effects of kidney donation on BP, and Doshi et al[15] reported BP to be higher in African American donors compared with African American controls. Similarly, using claims data from a private insurance database, Lentine et al[16] reported that African American donors had an increased risk of hypertension compared with white donors.

Few studies have reported 24-hour ambulatory BP in kidney donors, and none of these studies has included 2-kidney controls (Table S5).[17-22] In addition, follow-up after donation has been relatively short in most studies. Therefore, it is difficult from these studies to draw firm conclusions on the effects of donation on BP. Additional follow-up of the current cohort may be helpful in this regard.

Hyperuricemia has long been suggested to cause CKD,[23-27] hypertension,[28] diabetes,[29] and cardiovascular disease.[30-32] However, the reverse is equally plausible, that is, that hypertension, diabetes, and cardiovascular disease cause hyperuricemia by reducing kidney function. The current study confirms our earlier observation that a reduction in GFR most likely causes an increase in serum uric acid levels[4] and shows that this increase persists for at least 36 months after donation. Rossi et al[33] reported in 42 donors that urate levels increased from a mean of 0.29 ± 0.08 mmol/L predonation to 0.34 ± 0.08 mmol/L at 1 year and 0.34 ± 0.08 mmol/L at 2 years postdonation ($P < 0.001$ vs predonation at 1 and 2 years).

There have been similar anecdotal reports of increased uric acid levels after donation.[34] For example, Undurraga et al[35] reported that among 74 kidney donors followed up for a mean of 10.9 ± 4.5 years, uric acid levels > 7.5 g/dL occurred in 30%. Hida et al[36] reported that for 34 donors, uric acid levels increased 24.3% from a mean of 4.78 ± 1.26 mg/dL before donation to 5.88 ± 1.40 mg/dL 6 months to 5 years after donation. Romero et al[37] followed up 8 donors for 6 months after donation and found no increase in uric acid levels.

Previously, we found that between predonation and 6 months, there was no discernible effect of donation

Table 6. Laboratory Measurements at 6, 12, 24, and 36 Months After Kidney Donation

Test	Group	Visit (time after donation)				*P*[a]		
		6 mo	12 mo	24 mo	36 mo	Donors vs Controls[b]	Visit[c]	Interaction[d]
Hemoglobin (g/dL)	Controls	13.6 ± 1.4 (195)	13.4 ± 1.4 (191)	13.6 ± 1.2 (175)	13.6 ± 1.2 (173)	0.003	<0.001	0.02
	Donors	13.2 ± 1.2 (200)	13.1 ± 1.3 (197)	13.4 ± 1.3 (183)	13.5 ± 1.4 (172)			
Leukocyte count (/μL)	Controls	6.0 ± 1.7 (195)	6.1 ± 1.8 (190)	6.0 ± 1.6 (174)	6.0 ± 1.8 (157)	0.1	0.6	0.8
	Donors	5.8 ± 1.5 (200)	5.9 ± 1.8 (196)	5.7 ± 1.5 (182)	5.8 ± 1.6 (169)			
Serum albumin (mg/dL)	Controls	4.07 ± 0.33 (198)	4.03 ± 0.30 (193)	4.06 ± 0.32 (182)	4.02 ± 0.27 (173)	0.9	0.008	0.9
	Donors	4.06 ± 0.31 (200)	4.03 ± 0.30 (198)	4.05 ± 0.30 (185)	4.00 ± 0.27 (182)			
CRP (mg/dL)	Controls	1.4 [0.6-3.1] (198)	1.2 [0.5-2.8] (193)	1.2 [0.5-2.6] (182)	1.0 [0.6-2.4] (173)	0.7[e]	0.6[e]	0.01[e]
	Donors	1.2 [0.7-2.9] (200)	1.3 [0.6-2.5] (196)	1.1 [0.6-2.5] (185)	1.2 [0.6-3.0] (182)			
Fibrinogen (mg/dL)	Controls	305 ± 67 (198)	306 ± 74 (193)	311 ± 65 (182)	306 ± 67 (173)	0.8	0.2	0.3
	Donors	300 ± 72 (198)	310 ± 66 (196)	309 ± 81 (185)	309 ± 70 (181)			
Homocysteine (mg/L)	Controls	1.21 ± 0.34 (196)	1.21 ± 0.37 (193)	1.28 ± 0.43 (182)	1.23 ± 0.38 (173)	<0.001	0.6	0.05
	Donors	1.49 ± 0.43 (198)	1.46 ± 0.42 (196)	1.50 ± 0.42 (185)	1.41 ± 0.43 (182)			
Uric acid (mg/dL)	Controls	4.9 ± 1.2 (198)	4.9 ± 1.2 (193)	4.9 ± 1.2 (182)	5.0 ± 1.1 (173)	<0.001	<0.001	0.2
	Donors	5.3 ± 1.1 (200)	5.2 ± 1.2 (196)	5.4 ± 1.2 (185)	5.5 ± 1.3 (182)			
Serum potassium (mmol/L)	Controls	4.14 ± 0.32 (197)	4.10 ± 0.29 (187)	4.12 ± 0.31 (177)	4.11 ± 0.28 (172)	0.006	0.1	0.9
	Donors	4.20 ± 0.29 (199)	4.19 ± 0.35 (193)	4.20 ± 0.32 (181)	4.17 ± 0.27 (178)			
Serum calcium (mg/dL)	Controls	9.19 ± 0.38 (198)	9.18 ± 0.42 (193)	9.17 ± 0.41 (182)	9.21 ± 0.40 (173)	0.4	0.2	0.7
	Donors	9.24 ± 0.42 (200)	9.18 ± 0.41 (196)	9.24 ± 0.38 (185)	9.26 ± 0.40 (182)			
Serum phosphorus (mg/dL)	Controls	3.49 ± 0.48 (198)	3.55 ± 0.46 (190)	3.52 ± 0.46 (178)	3.51 ± 0.46 (172)	<0.001	0.007	0.003
	Donors	3.30 ± 0.48 (200)	3.37 ± 0.51 (195)	3.43 ± 0.51 (182)	3.42 ± 0.51 (178)			
PTH (pg/mL)	Controls	42.8 ± 15.6 (198)	42.4 ± 16.7 (193)	43.6 ± 16.3 (182)	43.2 ± 17.5 (173)	<0.001	0.7	0.3
	Donors	52.7 ± 20.9 (200)	52.9 ± 22.1 (196)	51.7 ± 20.6 (185)	52.5 ± 24.1 (182)			
Cholesterol (mg/dL)	Controls	186 ± 36 (197)	185 ± 37 (193)	188 ± 34 (182)	190 ± 35 (173)	0.9	0.01	0.8
	Donors	186 ± 35 (199)	184 ± 32 (195)	186 ± 36 (185)	188 ± 35 (182)			
LDL cholesterol (mg/dL)	Controls	111 ± 30 (193)	111 ± 30 (190)	113 ± 29 (182)	115 ± 30 (172)	0.7	0.03	0.1
	Donors	110 ± 31 (193)	108 ± 30 (194)	109 ± 30 (184)	111 ± 31 (180)			
HDL cholesterol (mg/dL)	Controls	54.9 ± 16.4 (195)	54.5 ± 15.9 (193)	56.8 ± 16.2 (182)	56.2 ± 16.0 (172)	0.9	<0.001	0.2
	Donors	54.1 ± 13.9 (197)	55.1 ± 14.2 (195)	56.6 ± 15.8 (185)	56.5 ± 15.0 (181)			
Triglycerides (mg/dL)	Controls	80 [59-119] (197)	77 [62-117] (193)	78 [59-104] (182)	76 [59-107] (173)	0.1[e]	0.1[e]	0.6[e]
	Donors	84 [64-124] (199)	81 [61-122] (195)	84 [65-127] (185)	89 [61-124] (182)			
Lipoprotein(a) (mg/dL)	Controls	16.0 [5.0-43.0] (198)	15.0 [5.0-44.0] (193)	15.0 [5.0-42.0] (182)	15.0 [5.0-45.0] (173)	0.3[e]	0.9[e]	0.4[e]
	Donors	20.0 [5.0-54.5] (200)	18.0 [5.0-51.5] (196)	20.0 [11.0-49.0] (185)	18.5 [10.0-45.0] (182)			
Hemoglobin A_{1c} (%)	Controls	5.3 ± 0.35 (195)	5.3 ± 0.34 (190)	5.4 ± 0.34 (181)	5.4 ± 0.33 (173)	0.1	<0.001	0.5
	Donors	5.3 ± 0.31 (197)	5.3 ± 0.38 (191)	5.3 ± 0.32 (181)	5.3 ± 0.33 (181)			
Glucose (mg/dL)	Controls	91.2 ± 8.94 (197)	91.1 ± 8.66 (193)	92.5 ± 9.23 (182)	93.2 ± 9.03 (173)	0.04	<0.001	0.7
	Donors	89.2 ± 8.51 (199)	90.7 ± 11.4 (195)	90.6 ± 8.72 (185)	91.4 ± 8.78 (182)			

(Continued)

Table 6 (Cont'd). Laboratory Measurements at 6, 12, 24, and 36 Months After Kidney Donation

Test	Group	Visit (time after donation)				P[a]		
		6 mo	12 mo	24 mo	36 mo	Donors vs Controls[b]	Visit[c]	Interaction[d]
Insulin (pmol/L)	Controls	39 [26-64] (192)	36 [24-54] (188)	39 [25-65] (174)	42 [29-64] (166)	0.9[e]	<0.001[e]	0.2[e]
	Donors	36 [24-54] (198)	41 [24-66] (194)	43 [30-63] (183)	43 [31-66] (171)			
HOMA-IR	Controls	1.5 [0.96-2.5] (191)	1.4 [0.88-2.2] (188)	1.5 [0.94-2.5] (174)	1.6 [1.1-2.6] (166)	0.7[e]	<0.001[e]	0.2[e]
	Donors	1.4 [0.91-2.1] (197)	1.4 [0.95-2.5] (193)	1.7 [1.0-2.3] (183)	1.6 [1.1-2.7] (171)			

Note: Values are given as mean ± standard deviation or median [interquartile range] (number sampled). Conversion factors for units: fibrinogen in mg/dL to µmol/L, ×0.0294; homocysteine in mg/L to µmol/L, ×7.397; uric acid in mg/dL to µmol/L, ×59.48; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129; glucose in mg/dL to mmol/L, ×0.05551.

Abbreviations and definitions: CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance, where log(HOMA IR) = log[(insulin × glucose)/22.5], with insulin in µU/mL and glucose in mmol/L; LDL, low-density lipoprotein; PTH, parathyroid hormone.

[a]Analysis of variance with repeated measures. Each variable was analyzed separately and no adjustment was made for multiple comparisons. Values not normally distributed were logarithmically transformed before analysis.

[b]Donors versus controls *P* values test overall differences between donors and controls.

[c]Visit *P* values test differences among the 4 visits.

[d]Interaction *P* values test the interaction between donors versus controls and between visits.

[e]Based on logarithmically transformed values.

on serum potassium levels.[4] However, with longer follow-up, there has been a small but statistically significant increase in serum potassium levels in donors compared with controls (Table 6). There were no changes in sodium, chloride, or carbon dioxide levels or urine pH (Table S6). To our knowledge, this is the first report of donation affecting serum potassium levels. The increase likely is too small to be relevant clinically. However, the increase could be problematic if a donor were to be challenged with additional factors that also increase serum potassium levels.

Cross-sectional studies suggest that CKD is associated with abnormalities in glucose homeostasis and insulin resistance.[38-43] However, in the present study, there was no effect of donation on fasting glucose, hemoglobin A_{1c}, or insulin concentrations or calculated HOMA-IR. Similarly, there were no differences in lipid concentrations that often accompany changes in insulin resistance (Table 6).

We previously reported an acute increase in homocysteine concentration after donation,[4] and the current study shows persistently elevated levels in donors compared with controls at 36 months. Tsai et al[44] reported that homocysteine levels increased in 10 donors from a mean of 8.2 ± 1.3 µmol/L predonation to 12.1 ± 4.4, 11.5 ± 2.6, and 10.3 ± 2.2 µmol/L at 2 days, 6 weeks, and 6 months, respectively (all $P < 0.05$ vs predonation). There is no evidence that increased homocysteine level has adverse consequences, and randomized trials consistently have not shown that reducing homocysteine levels improves patient outcomes.[45,46]

We found no difference between donors and controls in CRP levels (Table 6). Others have reported that inflammatory marker levels are elevated acutely after kidney donation. For example, Tsai et al[44] reported that CRP levels were increased at 2 days after surgery but had returned to predonation levels by 6 weeks postdonation. However, in contrast, Rossi et al[33] reported that in 42 donors, CRP levels increased from a median of 1.2 (IQR, 0.9-2.7) mg/dL predonation to 2.0 (IQR, 0.9-3.7) mg/dL and 2.1 (IQR, 1.5-3.3) mg/dL at 1 and 2 years postdonation, respectively ($P = 0.005$ vs predonation at 1 and 2 years).

Previous studies have suggested that kidney donors have mild proteinuria.[3] With 36 months of follow-up, donors in our study have urine total protein excretion similar to controls. Urine albumin excretion is lower in donors of our study compared with controls, but is increasing between 6 and 36 months, suggesting that longer follow-up is needed to determine whether kidney donation ultimately leads to increased urine albumin excretion. Potential markers of inflammation, including serum albumin, CRP, and fibrinogen concentrations, continue to be similar in donors and controls (Table 6). Hemoglobin levels are lower in

donors, but the gap appears to be narrowing with duration of follow-up.

We previously reported that serum parathyroid hormone concentrations were increased, phosphorus levels were reduced, and calcium levels were unchanged after donation.[4] The present study results confirm these findings and demonstrate that these differences persist 3 years after donation (Table 6). We previously discussed these changes in light of other published studies at that time,[47-52] but since then, Young et al[53] have reported on 198 living kidney donors and 98 nondonor controls assessed at a median of 5.3 years postdonation. They found that serum fibroblast growth factor 23 levels were significantly higher in donors compared with controls. Compared with controls, donors also had higher parathyroid hormone levels, higher renal tubular fractional excretion of inorganic phosphate, lower serum phosphate levels, and lower serum calcitriol concentrations. Additional controlled studies of donors may help elucidate the pathogenesis of these changes in donors, as well as in CKD.

Limitations of the present study include the fact that controls could not be screened as rigorously as donors for underlying kidney abnormalities, and it is possible that donors were healthier than controls. However, as previously noted,[4] more donors (31%) than controls (15%) were blood relatives of individuals with CKD. Follow-up is still relatively short, and it is possible that effects of donation may take much longer than 3 years to become manifest. For the analysis and interpretation of the many secondary end points, we did not undertake a statistical adjustment for multiple comparisons. This increases the possibility that some of the differences reported could be due to chance. Balanced against this is the prior probability from other studies reporting similar findings. In the end, given that an important objective of this study is to ensure donor safety, we opted not to adjust *P* values for multiple comparisons. It should be noted that 95% of participants in our study are white (Table S1), and the effects of donation may be different in other populations. Clearly, additional studies in higher risk populations are needed, as is longer follow-up. Finally, this study was not designed to have statistical power to examine outcomes of importance to donors, such as mortality and end-stage renal disease.

In summary, this study continues to provide important information about the pathophysiologic changes accompanying a reduction in kidney mass in apparently healthy individuals. The results confirm that the reduction in kidney function from donation leads to biochemical changes that may or may not ultimately have consequences important to donors. Prospective controlled studies of living kidney donors also afford a unique opportunity to better understand the consequences of reduced kidney function in patients with CKD. For all these reasons, the current study results suggest that additional prospective cohort studies should be undertaken. These studies should include adequate numbers of donors who may have isolated medical abnormalities or other plausible risk factors for adverse outcomes after kidney donation.

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SUPPLEMENTARY MATERIAL

Table S1: Demographic characteristics of study participants.

Table S2: Medication usage.

Table S3: BP medications and increased BP.

Table S4: Studies examining incidence of hypertension in donors vs controls.

Table S5: Results of studies of 24-hour ambulatory BP monitoring.

Table S6: Serum electrolytes and urine pH at 6, 12, 24, and 36 months after kidney donation.

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REFERENCES

1. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-2081.

2. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80(1):93-104.

3. Garg AX, Muirhead N, Knoll G, et al. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. *Kidney Int*. 2006;70(10):1801-1810.

4. Kasiske BL, Anderson-Haag T, Ibrahim HN, et al. A prospective controlled study of kidney donors: baseline and 6-month follow-up. *Am J Kidney Dis*. 2013;62(3):577-586.

5. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

6. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20-29.

7. Kit BK, Ogden CL, Flegal KM. Prescription medication use among normal weight, overweight, and obese adults, United States, 2005-2008. *Ann Epidemiol*. 2012;22(2):112-119.

8. Saran R, Marshall SM, Madsen R, Keavey P, Tapson JS. Long-term follow-up of kidney donors: a longitudinal study. *Nephrol Dial Transplant*. 1997;12(8):1615-1621.

9. Tent H, Sanders JS, Rook M, et al. Effects of preexistent hypertension on blood pressure and residual renal function after donor nephrectomy. *Transplantation*. 2012;93(4):412-417.

10. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol*. 1976;31:155-163.

11. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985;33(4):278-285.

12. Boudville N, Prasad GV, Knoll G, et al. Meta-analysis: risk for hypertension in living kidney donors. *Ann Intern Med*. 2006;145(3):185-196.

13. Garg AX, Prasad GV, Thiessen-Philbrook HR, et al. Cardiovascular disease and hypertension risk in living kidney donors: an analysis of health administrative data in Ontario, Canada. *Transplantation*. 2008;86(3):399-406.

14. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med*. 2009;360(5):459-469.

15. Doshi MD, Goggins MO, Li L, Garg AX. Medical outcomes in African American live kidney donors: a matched cohort study. *Am J Transplant*. 2013;13(1):111-118.

16. Lentine KL, Schnitzler MA, Xiao H, et al. Racial variation in medical outcomes among living kidney donors. *N Engl J Med*. 2010;363(8):724-732.

17. Eberhard OK, Kliem V, Offner G, et al. Assessment of long-term risks for living related kidney donors by 24-h blood pressure monitoring and testing for microalbuminuria. *Clin Transplant*. 1997;11(5, pt 1):415-419.

18. Siebels M, Theodorakis J, Schmeller N, et al. Risks and complications in 160 living kidney donors who underwent nephroureterectomy. *Nephrol Dial Transplant*. 2003;18(12):2648-2654.

19. Textor SC, Taler SJ, Driscoll N, et al. Blood pressure and renal function after kidney donation from hypertensive living donors. *Transplantation*. 2004;78(2):276-282.

20. Goto N, Uchida K, Morozumi K, et al. Circadian blood pressure rhythm is disturbed by nephrectomy. *Hypertens Res*. 2005;28(4):301-306.

21. Prasad GV, Lipszyc D, Huang M, Nash MM, Rapi L. A prospective observational study of changes in renal function and cardiovascular risk following living kidney donation. *Transplantation*. 2008;86(9):1315-1318.

22. Ramesh Prasad GV, Lipszyc D, Sarker S, Huang M, Nash MM, Rapi L. Twenty four-hour ambulatory blood pressure profiles 12 months post living kidney donation. *Transpl Int*. 2010;23(8):771-776.

23. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res*. 2001;24(6):691-697.

24. Obermayr RP, Temml C, Knechtelsdorfer M, et al. Predictors of new-onset decline in kidney function in a general middle-european population. *Nephrol Dial Transplant*. 2008;23(4):1265-1273.

25. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol*. 2008;19(6):1204-1211.

26. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med*. 2009;169(4):342-350.

27. Ben-Dov IZ, Kark JD. Serum uric acid is a GFR-independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. *Nephrol Dial Transplant*. 2011;26(8):2558-2566.

28. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2011;63(1):102-110.

29. Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care*. 2009;32(9):1737-1742.

30. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum*. 2009;61(7):885-892.

31. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2010;62(2):170-180.

32. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359(17):1811-1821.

33. Rossi M, Campbell KL, Johnson DW, et al. Uremic toxin development in living kidney donors: a longitudinal study. *Transplantation*. 2014;97(5):548-554.

34. Young A, Nevis IF, Geddes C, et al. Do biochemical measures change in living kidney donors? A systematic review. *Nephron Clin Pract*. 2007;107(3):c82-c89.

35. Undurraga A, Roessler E, Arcos O, et al. Long-term follow-up of renal donors. *Transplant Proc*. 1998;30(5):2283-2285.

36. Hida M, Iida T, Shimbo T, et al. Renal function after nephrectomy in renal donors. *Tokai J Exp Clin Med*. 1982;7(4):511-516.

37. Romero RR, Alberu J, Correa-Rotter R, Vargas-Vorackova F, Isordia-Salas I, Majluf-Cruz A. Serum erythropoietin levels in kidney donors after renal transplantation. *Transplantation*. 2000;70(2):386-387.

38. Dzurik R, Spustova V, Janekova K. The prevalence of insulin resistance in kidney disease patients before the development of renal failure. *Nephron*. 1995;69(3):281-285.

39. Eidemak I, Feldt-Rasmussen B, Kanstrup IL, Nielsen SL, Schmitz O, Strandgaard S. Insulin resistance and hyperinsulinaemia in mild to moderate progressive chronic renal failure and its association with aerobic work capacity. *Diabetologia*. 1995;38(5):565-572.

40. Vareesangthip K, Tong P, Wilkinson R, Thomas TH. Insulin resistance in adult polycystic kidney disease. *Kidney Int*. 1997;52(2):503-508.

41. Fliser D, Pacini G, Engelleiter R, et al. Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int*. 1998;53(5):1343-1347.

42. Kubo M, Kiyohara Y, Kato I, et al. Effect of hyperinsulinemia on renal function in a general Japanese population: the Hisayama study. *Kidney Int*. 1999;55(6):2450-2456.

43. Kato Y, Hayashi M, Ohno Y, Suzawa T, Sasaki T, Saruta T. Mild renal dysfunction is associated with insulin resistance in chronic glomerulonephritis. *Clin Nephrol*. 2000;54(5):366-373.

44. Tsai MY, Aras O, Sozen H, et al. Plasma homocysteine levels in living kidney donors before and after uninephrectomy. *J Lab Clin Med*. 2004;143(6):340-343.

45. Clarke R, Halsey J, Lewington S, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37 485 individuals. *Arch Intern Med*. 2010;170(18):1622-1631.

46. Jardine MJ, Kang A, Zoungas S, et al. The effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease: systematic review and meta-analysis. *BMJ*. 2012;344:e3533.

47. Pabico RC, McKenna BA, Freeman RB. Renal function before and after unilateral nephrectomy in renal donors. *Kidney Int*. 1975;8(3):166-175.

48. Friedlander MA, Lemke JH, Horst RL. The effect of uninephrectomy on mineral metabolism in normal human kidney donors. *Am J Kidney Dis*. 1988;11(5):393-401.

49. Gonzalez R, Butt KMH, Sumrani N, Tejani A. Long-term renal, endocrine, and hematologic evaluation of kidney donors. *Transplant Proc*. 1989;21(1):1946-1948.

50. Gossmann J, Wilhelm A, Kachel HG, et al. Long-term consequences of live kidney donation follow-up in 93% of living kidney donors in a single transplant center. *Am J Transplant*. 2005;5(10):2417-2424.

51. Bieniasz M, Kwiatkowski A, Domagala P, et al. Serum concentration of vitamin D and parathyroid hormone after living kidney donation. *Transplant Proc*. 2009;41(8):3067-3068.

52. Westerberg PA, Ljunggren O, Larsson TE, Wadstrom J, Linde T. Fibroblast growth factor-23 and mineral metabolism after unilateral nephrectomy. *Nephrol Dial Transplant*. 2010;25(12):4068-4071.

53. Young A, Hodsman AB, Boudville N, et al. Bone and mineral metabolism and fibroblast growth factor 23 levels after kidney donation. *Am J Kidney Dis*. 2012;59(6):761-769.