AJKD

Original Investigation

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

Bertram L. Kasiske, MD,[1] Teresa Anderson-Haag, PharmD, BCPS,[1] Ajay K. Israni, MD,[1] Roberto S. Kalil, MD,[2] Paul L. Kimmel, MD,[3] Edward S. Kraus, MD,[4] Rajiv Kumar, MD,[5] Andrew A. Posselt, MD,[6] Todd E. Pesavento, MD,[7] Hamid Rabb, MD,[4] Michael W. Steffes, MD,[8] Jon J. Snyder, PhD,[9] and Matthew R. Weir, MD[10]

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.

Am J Kidney Dis. ■(■):■-■. © *2015 by the National Kidney Foundation, Inc.*

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).

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 for donors has been problematic. We reported the

From the [1]Department of Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis, MN; [2]Department of Medicine, University of Iowa, Iowa City, IA; [3]Division of Kidney Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda; [4]Department of Medicine, Johns Hopkins University, Baltimore, MD; [5]Department of Medicine, Mayo Clinic, Rochester, MN; [6]Department of Surgery, University of California at San Francisco, San Francisco, CA; [7]Department of Medicine, Ohio State University, Columbus, OH; [8]Department of Laboratory Medicine and Pathology, University of Minnesota; [9]Scientific Registry of Transplant Recipients, Minneapolis Medical Research Foundation, Minneapolis, MN; and [10]Division of Nephrology, Department of Medicine, University of Maryland, School of Medicine, Baltimore, MD.

Received October 7, 2014. Accepted in revised form January 25, 2015.

Address correspondence to Bertram L. Kasiske, MD, Department of Medicine, Hennepin County Medical Center, 701 Park Ave, Minneapolis, MN 55415. E-mail: bkasiske@cdrg.org

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.01.019

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