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A Prospective Controlled Study of Kidney Donors: Baseline and 6-Month Follow-up

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Abstract

Background—Most previous studies of living kidney donors have been retrospective and have lacked suitable healthy controls. Needed are prospective controlled studies to better understand the effects of a mild reduction in kidney function from kidney donation in otherwise normal individuals.

Study Design—Prospective, controlled, observational cohort study.

Setting & Participants—Consecutive patients approved for donation at 8 transplant centers in the US were asked to participate. For every donor enrolled, an equally healthy control with 2 kidneys who theoretically would have been suitable to donate a kidney was also enrolled.

Predictor—Kidney donation.

Measurements—At baseline pre-donation and at 6 months after donation, a medical history, vital signs, measured (iohexol) glomerular filtration rate and other measurements were collected.

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There were 201 donors and 198 controls that completed both baseline and 6 month visits and form the basis of this report.

Results—Compared to controls, donors had 28% lower glomerular filtration rate at 6 months (94.6±15.1 [SD] v. 67.6±10.1 mL/min/1.73m^2; P<0.001), associated with a 23% greater parathyroid hormone (42.8±15.6 v. 52.7±20.9 pg/mL; P<0.001), 5.4% lower serum phosphate (3.5±0.5 v. 3.3±0.5 mg/dL; P<0.001), 3.7% lower hemoglobin (13.6±1.4 v. 13.1±1.2 g/dL; P<0.001), 8.2% greater uric acid (4.9±1.2 v. 5.3±1.1 mg/dL; P<0.001), 24% greater homocysteine (1.20±0.34 v. 1.49±0.43 mg/L; P<0.001), and 1.5% lower high density lipoprotein cholesterol (54.9±16.4 v. 54.1±13.9 mg/dL; P=0.03) level. There were no differences in albumin-creatinine ratios (5.0 [IQR, 4.0-6.6] v. 5.0 [IQR, 3.3-5.4] mg/g; P=0.5), office blood pressure, or glucose homeostasis.

Limitations—Short duration of follow-up and possible bias resulting from an inability to screen controls with kidney and vascular imaging performed in donors.

Conclusions—Kidney donors have some, but not all, abnormalities typically associated with mild chronic kidney disease 6 months after donation. Additional follow up is warranted.

The shortage of deceased donor kidneys has led to the widespread use of living kidney donors. A number of retrospective studies have reported that short and long term outcomes for living kidney donors are excellent.[1] However, these studies have several important limitations. First, they generally fail to locate all donors who have donated, and the donors who cannot be located may be more likely to have had worse outcomes. Second, many studies do not have a suitable control group. Donors are carefully screened and selected to be healthy, and reports that donors are healthy on follow-up could be biased if donors are compared to the general population, or to controls that were not as rigorously screened as donors. Indeed, the findings that donors live longer than individuals from the general population result from a lack of suitable controls and not from kidney donation prolonging life.[2, 3] Finally, most donors enrolled in retrospective studies donated in an era when selection criteria were more restrictive than they are today.

We designed a multicenter prospective study in which each living donor enrolled with an equally healthy control with 2 kidneys. By including healthy controls, this study permits a better assessment of potential harms to kidney donors, and thereby provides important information for informing future donors and recipients of the risk of donation. In addition, the present study will allow us to measure parameters reported to be abnormal in patients with mild chronic kidney disease (CKD) in normal kidney donors to determine whether mild reductions in kidney function *per se* cause abnormalities. In this report we describe the study, and the results of baseline and 6 month follow-up visits.

METHODS

Human Subject Protections

Informed consent was obtained from each participant, and the study was approved by the Institutional Review Board at each participating site (University of Minnesota number 0503M67993). In addition, an External Advisory Committee met on August 29, 2006; June 11, 2007; February 20, 2008; December 2, 2009; and May 24, 2011. The External Advisory Committee reviewed the protocol and all revisions, and made recommendations regarding the conduct of the study.

Study Design

This prospective, observational, cohort study was designed and funded for 5 years. Enrollment was to be completed by 2 years, leaving at least 3 years for follow-up. Donors

were enrolled after acceptance for donation, but before the actual donation had taken place. For every donor enrolled, 1 control was also enrolled. Donors and controls completed a baseline pre-donation visit, and visits at 6, 12, 24 and 36 months after donation.

Inclusion Criteria

Initially, individuals selected to be living kidney donors, who were not blood-related or who were only distantly blood-related to the intended recipient, were asked to participate if they also had a healthy sibling that was willing to participate as a control. The goal was to continue recruitment until 200 pairs of donors and controls had completed baseline and 6-month post-donation visits. The first participant completed a baseline visit July 18, 2006. However, 1 year later only 23 pairs had enrolled. At that time the study protocol was amended to enhance enrollment by recruiting *any* potential living kidney donor. Controls could be *any* healthy individual who could theoretically be a donor at the study site, not just siblings of enrolled donors. Controls were screened with medical history, vital signs and basic laboratory tests for kidney disease, but did not undergo other screening tests that may have been performed on donors. Thus, there may have been some bias for donors to be healthier than controls. The last participant completed a baseline study visit February 25, 2011, and enrollment took 4½ years, instead of 2 years as originally planned. Some potential donors completed baseline visits, but did not donate. These donors and their controls were replaced.

Exclusion Criteria

Exclusion criteria for both donors and controls included: 1) unable or unwilling to give informed consent, 2) allergy to intravenous radiocontrast or seafood, and 3) age younger than 18 years. In addition, any living kidney donor exclusion criteria applicable for donors at the study site were also applicable to controls at that site. These generally included evidence of kidney disease (especially proteinuria), invasive cancer, active infection, cardiovascular disease, diabetes, and psychiatric disorders.[4] Women of child-bearing potential but not pregnant were allowed to participate, but underwent screening for pregnancy before each study visit, and were not administered iohexol if/when they became pregnant.

Participating Study Sites

There were initially 7 sites: the University of Minnesota, Minneapolis, MN; Hennepin County Medical Center, Minneapolis, MN; the Mayo Clinic, Rochester, MN; the University of Maryland, Baltimore, MD, the Johns Hopkins School of Medicine, Baltimore, MD, the Ohio State University, Columbus, OH, and the University of Alabama, Birmingham, AL. However, the University of Alabama ended their participation before enrolling any subjects. The University of Iowa, Iowa City, IA; and the University of California at San Francisco were subsequently added.

Data Collected

Before donation (baseline) and 6 months after donation participants were evaluated in the Clinical Research Center at each participating site. A complete medical history was obtained. After subjects were seated and resting for at least 5 minutes, blood pressure and heart rate were measured 3 times at 1 minute intervals using the right arm (raised to heart level) while they were sitting with feet flat on the floor and resting quietly. Height, body weight, waist and hip circumference were measured. Blood and urine samples were obtained after an overnight fast. A complete blood count and urinalysis were performed at the site's clinical laboratory. Whole blood, serum and plasma samples were also sent to the University of Minnesota Advanced Research and Diagnostic Laboratory for fasting glucose, serum electrolytes, calcium, albumin, urea nitrogen, and serum creatinine, cystatin C, total

cholesterol, high-density lipoprotein cholesterol, calculated low-density lipoprotein cholesterol triglycerides, lipoprotein(a), homocysteine, glycated hemoglobin A1c, insulin, phosphorus, parathyroid hormone (PTH), uric acid, high-sensitivity C-reactive protein, and fibrinogen analyses and for storage at –70°C. A random morning void was used to obtain urine dipstick results. In addition, 4 one mL aliquots of urine were placed into each of 4 clear-capped plastic tubes and frozen: 1 for urine protein-creatinine and albumin-creatinine ratios, and 3 saved specimens, frozen at –70°C. All were transported with dry ice to the Central Laboratory.

Insulin was measured in serum or EDTA plasma on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a sandwich immunoassay method (Roche Diagnostics Corporation). Intact PTH was measured in serum or EDTA plasma on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a sandwich immunoassay method (Roche Diagnostics). Cystatin C was determined nephelometrically in serum or plasma initially using the Dade Behring BN100 (Dade Behring, Inc.) nephelometer. In 2012 samples were assayed using the Gentian® immunoassay (Gentian AS, Moss, Norway), which was more closely aligned to an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Reference Material (European Reference Material-DA471/IFCC).[5] All values (including those previously assayed by the Dade-Behring assay) were re-expressed and traceable to the IFCC Reference Material. Total homocysteine was measured in serum or plasma using liquid chromatography (Alliance 2795 HPLC Separations Module equipped with an autosampler and column oven [Waters Corp]) followed by tandem mass spectrometry.

An iohexol plasma decay method was used to measure glomerular filtration rate (mGFR). A heparin lock was placed in each arm. Slowly, but within 2 minutes, 5 mL of iohexol (Omnipaque™, GE Healthcare, Inc., Princeton, NJ) were injected, and the catheter was flushed with 10 mL of normal saline. Blood samples were drawn from the opposite arm 120, 150, 180, 210 and 240 minutes later with heparinized plasma separated from each sample. GFR was measured from the plasma decay of iohexol using the Brøchner-Mortensen method.[6] Iohexol was measured in plasma using a Thermo Scientific SpectraSYSTEM™ liquid chromatography system (Thermo Separation Products, Inc.) which consists of a P1000 LC pump coupled with an AS3000 autosampler and UV1000 detector. Chromatographic separation was achieved by means of a Supelcosil™ LC-18-DB column (Supelco/Sigma-Aldrich Co., LLC,) with detection at 254 nm. The laboratory interassay coefficient of variation is 2.7%.

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were used to calculate estimated glomerular filtration rate (eGFR), specifically the CKD-EPI creatinine equation from 2009 (yielding $eGFR_{cr}$)[7] as well as the CKD-EPI cystatin C and CKD-EPI creatinine–cystatin C equations[8] published in 2012 (generating $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$, respectively).

Statistical Analysis

The primary endpoint of this study is designated to be the difference between donors and controls in the slope of the mGFR measured by iohexol clearance between 6 and 36 months after donations. We estimated that to have 80% power to detect a within-donor difference between donors and controls of 5% in mGFR (approximately 3.25 mL/min/1.73m^2) the study would require 195 donors using a two-sided paired t-test and assuming a correlation of 0.6 between measurements from the same individual. This determination was used to select the sample size of the study.

Differences between groups and among 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 baseline versus 6 months post-donation, and the interaction between these two effects. Results were considered statistically significant for $P<0.05$, although consideration should be given to the fact that P-value was not adjusted for multiple comparisons. Variables that were not normally distributed were logarithmically transformed before analysis. Differences in categorical variables between groups and among visits were assessed with Chi-Square. All analyses were carried out with SAS® 9.2 for the personal computer (SAS Institute Inc, Cary, NC).

Results

Enrollment and Study Visits

Two hundred twenty-two pairs started the study and completed the baseline pre-donation visit (Table 1). Some potential donors did not donate. In 19 pairs one or both failed to complete a post-donation follow-up visit. However, 203 pairs completed at least one follow-up visit. In 5 cases (2 donors and 3 controls) the 6 month visit was missed and the first follow-up visit was at 12 months. An additional 6 pairs discontinued after completing 6 month follow-up visits. Midway through the study a decision was made to allow one of a pair to continue in the study if the other decided to discontinue, and to date 2 controls have dropped out despite their paired donors continuing. Thus, as of June 1, 2012, there were 203 donors and 201 controls still actively participating. However, in this report we include only baseline and 6 month visits. All of the anticipated baseline and 6 month visits have been completed (Table 2).

Participant Characteristics at Enrollment

Donor demographics were similar to those of controls (Table 3). However, donors differed from donors in the US as a whole. In particular, fewer African American and other minority donors enrolled in the study compared to donors in the US. Indeed, 95% of study donors were white compared to 70% of donors across the US. Some of this difference can be explained by the location of the study sites. In the states where sites were located, 86% of living kidney donors were white (Table 3). Study participants were more likely to be women and slightly older than living kidney donors in the states where the study sites were located and in the US. Mean donors age was 43.4±11.9 (standard deviation) years compared to 43.1±11.9 years for controls (P=0.8). Donors and controls had similar past medical histories, tobacco use histories, family histories and medication use at baseline (Table 4). Only 31% of donors had a first degree relative with CKD, but this was twice that of controls (Table 4).

Blood Pressure, Heart Rate, and Body Size

Heart rate and systolic blood pressure were not different between donors and controls, both declining slightly between baseline and 6 month visits (Table 5). There were no differences between donors and controls in diastolic blood pressure. There was no statistically significant difference in body weight between donors and controls at 6 months (P=0.06). Waist circumference declined in donors versus controls at 6 months (P=0.02), but there were no differences in body mass index between groups or visits. Approximately 20% of donors and controls were obese at the time of enrollment, with no difference between donors and controls (Table 6).

Kidney Function

The mGFR was 28% lower 6 months after donation (Table 6). Neither the urine total protein nor urine albumin was affected by donation at 6 months of follow-up.

Laboratory Parameters

Serum albumin concentration was slightly higher among donors compared to controls at baseline, but declined more in donors than controls after surgery (Table 7). C-reactive protein and fibrinogen concentrations were not affected by donation. Uric acid and homocysteine concentrations increased in kidney donors. Hemoglobin concentration was significantly lower in donors at the 6 month visit. Total cholesterol and low-density lipoprotein cholesterol were unaffected by donation. While high-density lipoprotein cholesterol was significantly reduced, changes in triglyceride concentrations were not statistically significant. Lipoprotein(a) concentrations did not change with donation. Parathyroid hormone increased in donors, while serum phosphorus declined slightly. Serum total calcium concentration did not change. Donation had no effect on serum sodium, potassium, chloride or carbon dioxide (data not shown).

DISCUSSION

There have been many studies of kidney donors but very few have been truly prospective and even fewer have had a suitable control group. Garg and coworkers conducted a systematic review of studies with at least 10 adult kidney donors followed at least 1 year after donation that measured kidney function and/or urine protein.[1] They identified 48 studies published from 1973 to November 2005. However, only 10 (21%) studies followed donors prospectively; only 1 of these had a suitable control group (and even this study[9] did not follow the controls prospectively from the time of donation). We searched MEDLINE and EMBASE for studies published since the systematic review of Garg and coworkers.[1] We excluded duplicate publications and located 21 new studies.[2,10-29] However, only 2 were prospective and neither had a control group.[13, 21]

The controls in the current study were comparable to the kidney donors by all parameters measured (Tables 3-7). Unfortunately, there were few ethnic minorities among donors and controls. Hence, the results of this study may not be applicable to other populations. In particular, concerns about the effects of reduced GFR among African American kidney donors cannot be addressed by this study.[16, 30, 31] Similarly, few participants in this study were obese.

There are a number of important findings in this study. The increase in PTH is in keeping with the correlation between PTH and kidney function reported in patients with mild CKD. Serum total calcium concentration was unchanged while serum phosphorus was reduced. In 1975 Pabico and co-workers noted decreased tubular reabsorption of phosphorus at 10 to 14 days after nephrectomy in 7 healthy donors.[32] Friedlander, et al., found that 17 donors had reduced tubular reabsorption of phosphate at 1 and 6 months after donation, and this was associated with an increase in carboxyl-terminal PTH.[33] Other cross-sectional studies have reported reduced 1,25-Dihydroxyvitamin D,[34] and increased fibroblast growth factor-23 (FGF-23).[35] In a recent cross-sectional study Young and co-workers found increased FGF-23, which correlated with the decline in eGFR in donors. In the Young study vitamin D and serum phosphate concentrations were reduced, while the fractional excretion of phosphate was increased compared to in healthy controls.[36] In the current study vitamin D concentrations and FGF-23 were not measured. Additional longitudinal studies are needed to determine how the decline in kidney function after donation leads to elevated PTH and reduced phosphorus concentrations, and what role vitamin D and FGF-23 play in these alterations.

It has previously been reported that patients with CKD have abnormalities in lipoprotein metabolism, including elevated triglycerides and reduced high-density lipoprotein cholesterol.[37, 38] However, it has been unclear from uncontrolled observational studies the

extent to which these lipid alterations were due to reduced kidney function *per se* or to the underlying causes of CKD. The current study indicates that the mild reduction in kidney function resulting from donor nephrectomy caused a decline in high-density lipoprotein cholesterol, but no statistically significant changes in triglycerides, low-density lipoprotein cholesterol or lipoprotein(a).

Hyperuricemia has long been suggested to cause CKD,[39-43] hypertension,[44] diabetes,[45], and cardiovascular disease[46-48]. However, this has been a source of ongoing controversy because it is possible that hypertension, diabetes and cardiovascular disease directly or indirectly cause hyperuricemia, resulting in so-called “reverse causation”. The current study unequivocally shows that a reduction in GFR causes a significant increase in serum uric acid, even in otherwise healthy individuals. Thus, whatever other factors may be causing an association between CKD and hyperuricemia, the reduction in GFR itself may explain much or all of the observed association.

Cross-sectional studies suggest that CKD is associated with abnormalities in glucose homeostasis and insulin resistance.[49-54] However, it is again unclear whether altered kidney function or underlying causes of CKD result in these abnormalities. In the present study there were no differences between donors and controls in fasting glucose, hemoglobin A1c, insulin concentrations, or the calculated homeostasis model assessment of insulin resistance. These data suggest that short term mild reductions in kidney function resulting from kidney donation do not cause alterations in glucose homeostasis or insulin resistance.

In the current study hemoglobin was significantly lower in donors 6 months after donation compared to controls (Table 7). We are not aware of this previously being reported. Possible explanations include mild anemia due to surgical blood loss, iron deficiency, and/or reduced erythropoietin due to the reduced kidney function. Whether this resolves with time remains to be determined.

Cross-sectional observational studies have shown a correlation between reduced kidney function and increased homocysteine concentrations.[55-57] The current study provides conclusive evidence that a mild reduction in kidney function indeed causes increases in homocysteine concentrations. Nevertheless, recent randomized trials have failed to show that reducing homocysteine improves patient outcomes.[58, 59] It is therefore unclear whether elevated homocysteine is harmful.

Several studies have suggested that kidney donors have mild proteinuria.[1] It is interesting therefore that there were no differences between donors and controls in urine total protein or albumin-creatinine ratios in the current study. Similarly, a number of investigations have suggested that blood pressure is mildly elevated in kidney donors.[60] However, blood pressure in the current study was not different between donors versus controls. The lack of differences in protein excretion and blood pressure could reflect the short term follow-up in the current study.

Although there were statistically significant effects of donation on serum albumin concentration, these effects were small and difficult to interpret (Table 7). At baseline, serum albumin concentration was numerically higher in donors than controls, declining to control levels at 6 months. It is difficult to conclude with certainty that donation caused a significant reduction in serum albumin concentration. Additional follow up may help to clarify these changes. It is noteworthy that several other biomarkers of inflammation were not affected by donation. In particular, C-reactive protein and fibrinogen concentrations were unchanged after donation (Table 7). These results, if sustained over time, may suggest that the putative inflammatory state associated with mild CKD may not be the result of a decline in kidney function so much as the underlying disease and the causes of CKD.

The decline in mGFR at 6 months was similar to that reported by others using various inert markers of GFR.[61-70] It is noteworthy that estimating equations using creatinine and/or cystatin C produced results similar to those of the pre- and post-donation measured GFR. These equations slightly over-estimated mGFR before donation and mGFR in controls with normal kidney function, but this bias was less apparent among donors after donation (Table 7). Long term follow up may help to determine whether changes in eGFR accurately reflect changes in GFR measured by iohexol, and which formulation may be most accurate.

There are some important limitations to this study. The controls could not be subjected to the same rigorous screening process that donors underwent, and therefore it is possible that controls were healthier than donors in ways not reflected by the study measurements reported here. On the other hand, more donors (31%) than controls (15%) were blood-relatives of individuals with CKD (Table 4), which could predispose the donors to CKD themselves. Finally, a relatively large number of variables were examined, making it possible that some differences in results were due to chance (type 1 statistical error). Therefore, it will be important to confirm these results in other studies, if possible.

In summary, the short term results of this study demonstrate that a number of physiological changes associated with CKD are found in donors with mild declines in GFR. However, a number of the reported changes wrought by CKD, such as increased blood pressure, were not found in kidney donors. This on-going study offers a unique opportunity to examine the effects of donation with its mild-to-moderate reductions in GFR on parameters of interest in patients with CKD. It will thereby help us understand the consequences of CKD as well as the safety of kidney donation.

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Table 1

Enrollment history (number of study pairs).

Study Site	Started[1]	Failed[2]	Enrolled[3]	Dropped[4]	Remained[5]
University of Minnesota	59	-6	53	-1	52
Hennepin County Medical Center	47	-1	46	-2	44
The Ohio State University	34	-2	32	-1	31
University of Maryland	30	-3	27	0	27
The Mayo Clinic, Rochester	23	-3	20	-2	18
Johns Hopkins University	16	-3	13	0	13
University of Iowa	7	0	7	0	7
University of California at San Francisco	6	-1	5	0	5
Total	222	-19	203	-6	197

[1] Pairs with both completing baseline (pre-donation) visits.

[2] Pairs with one or both who did not complete a follow-up visit.

[3] Pairs with both completing 6-month visits.

[4] Pairs that dropped out after completing 6-month visits.

[5] Pairs that remained after completing 6-month visits.

Table 2

Visits completed as of July 1, 2012.

Visit	Controls (n=201)	Donors (n=203)
Baseline	201 (100%)	203 (100%)
6 mo	198 (98.5%)	201 (99.0%)
12 mo	192 (95.5%)	198 (97.5%)
24 mo	157 (78.1%)	160 (78.8%)
36 mo	108 (53.7%)	110 (54.2%)

Note: Values are given as number (percentage)

Table 3

Demographic characteristics of study participants compared to regional and US donors during the same time period (2006-2010).

	Controls (n=201)	Donors (n=203)	Study States[1]	United States[2]
Male sex	32.3%	32.0%	40.3%	39.8%
White ethnicity	95.0%	94.6%	85.7%	69.7%
Age				
18-34 y	30.9%	28.1%	33.4%	33.2%
35-49 y	35.3%	40.9%	42.8%	44.6%
50-64 y	31.3%	28.6%	21.9%	20.9%
≥65 y	2.5%	2.5%	1.8%	1.3%

Note:Values are given as percentages.

[1]Restricted to living kidney donors in the states with participating sites (Minnesota, Ohio, Maryland, Iowa, and California), weighted by the proportion of donors enrolled in those states.

[2]All living donors in the US that donated, 2006-2010.

Table 4

Participant characteristics at baseline.

Participant Characteristic	Controls (n=201)	Donors (n=203)	P-Value[1]
Past medical history			
Hypertension	9 (4.5%)	6 (3.0%)	0.4
Hyperlipidemia	7 (3.5%)	7(3.5%)	0.9
Diabetes mellitus	0 (0.0%)	0 (0.0%)	0.3
Coronary heart disease	0 (0.0%)	1 (0.5%)	0.5
Cerebral vascular accident	0 (0.0%)	0 (0.0%)	0.9
Chronic kidney disease	1 (0.5%)	0 (0.0%)	0.5
Tobacco use			0.8
Never	132 (65.7%)	139 (68.5%)	
Former	45 (22.4%)	40 (19.7%)	
Current	24 (11.9%)	24 (11.8%)	
Medical history of a parent, sibling, or child			
Chronic kidney disease	30 (14.9%)	63 (31.0%)	<0.001
Hypertension	90 (44.8%)	100 (49.3%)	0.4
Diabetes	54 (26.9%)	66 (32.5%)	0.2
Acute myocardial infarction	40 (19.9%)	41 (20.2%)	0.9
Coronary revascularization	44 (21.9%)	42 (20.7%)	0.8
Cerebral vascular accident	27 (13.4%)	28 (13.8%)	0.9
Cardiovascular disease	77 (38.3%)	78 (38.4%)	0.9
Medication			
Anti-depressant	26 (12.9%)	27 (13.3%)	0.9
Lipid-lowering agent	31 (15.4%)	23 (11.3%)	0.2
Anti-hypertensive agent	10 (5.0%)	10 (4.9%)	0.9
Aspirin	14 (7.0%)	16 (7.9%)	0.7
Non-steroidal anti-inflammatory agent	10 (5.0%)	6 (3.0%)	0.3
Thyroid replacement	8 (4.0%)	11 (5.4%)	0.5
Hormone replacement or birth control*	29 (21.8%)[2]	16 (11.6%)[2]	0.02
Vitamin(s)	49 (24.4%)	50 (24.6%)	0.9
Calcium supplement	18 (9.0%)	9 (4.4%)	0.07
Other	58 (28.9%)	69 (34.0%)	0.3

Note: Values are given as number (percentage).

[1] By chi-square, or (if <10 per cell) Fisher's exact test.

[2] Among women only.

Table 5

Blood pressure, heart rate, and body size.

Variable	Baseline Visit		6-Mo Visit		*P* [2]		
	Controls (n=201)	Donors (n=203)	Controls (n=198)	Donors (n=201)	Controls vs Donors [3]	Baseline vs 6 Mo [4]	Interaction [5]
Heart rate (bpm)	68.0±9.9 (n=201)	67.6±10.5 (n=194)	66.2±10.0 (n=198)	66.4±10.2 (n=200)	0.6	0.003	0.5
Systolic blood pressure (mm Hg)	117±13 (n=201)	117±12 (n=198)	116±12 (n=198)	115±11 (n=199)	0.8	0.003	0.3
Diastolic blood pressure (mm Hg)	70.4±9.0 (n=201)	70.3±8.8 (n=198)	70.0±8.5 (n=198)	70.3±8.5 (n=199)	0.9	0.6	0.5
Body weight (kg)	77.7±17.1 (n=199)	77.0±14.8 (n=199)	78.0±17.3 (n=197)	76.8±15.2 (n=199)	0.6	0.6	0.06
Body mass index (kg/m^2)	26.9±5.1 (n=199)	26.8±4.2 (n=199)	27.0±5.3 (n=197)	26.8±4.3 (n=199)	0.8	0.3	0.3
Waist circumference (cm)	87.3±12.8 (n=181)	88.0±12.2 (n=175)	88.0±13.6 (n=179)	87.2±12.1 (n=181)	0.7	0.9	0.02

Note: Values are given as mean ± standard deviation (number analyzed). Numbers smaller than 202 reflect missing values.

[2] Analysis of variance with repeated measures. Each variable was analyzed separately and no adjustment was made for multiple comparisons.

[3] Controls v. donors P-values test overall differences between donors and controls.

[4] Baseline v. 6-month P-values test overall differences between baseline (pre-donation) and 6-month visits.

[5] Interaction P-values test the interaction between donors v. controls and baseline v. 6-month visits.

Table 6

Obesity among controls and donors at enrollment.

Obesity Index[a]	Controls (n=201)	Donors (n=203)
Normal, <25.0 kg/m^2	84 (41.8%)	72 (35.5%)
Overweight, 25.0-29.9 kg/m^2	70 (34.8%)	83 (40.9%)
Obese, 30.0-39.9 kg/m^2	41 (20.4%)	42 (20.7%)
Massively obese, ≥40.0 kg/m^2	4 (2.0%)	2 (1.0%)
Missing/could not be calculated	2 (1.0%)	4 (2.0%)

Note: Values are given as number (percentage). P=0.5 by Chi-Square.

[a]Body mass index given after the comma.

Table 7

Laboratory values.

Variable	Baseline Visit		6-Mo Visit		*P* [2]		
	Controls	Donors	Controls	Donors	Controls vs Donors [3]	Baseline vs 6 mo [4]	Interaction [5]
mGFR (mL/min)	106.5±19.3 (n=186)	106.7±18.6 (n=181)	104.9±20.2 (n=194)	74.3±12.9 (n=193)	0.8	<0.001	<0.001
mGFR (mL/min/1.73m^2)	96.9±15.3 (n=186)	96.9±15.3 (n=181)	94.6±15.1 (n=194)	67.6±10.1 (n=193)	0.5	<0.001	<0.001
SCr (mg/dL)	0.79±0.15 (n=200)	0.80±0.15 (n=199)	0.80±0.17 (n=198)	1.16±0.22 (n=199)	0.8	<0.001	<0.001
$eGFR_{cr}$ (mL/min/1.73m^2)	100.1±16.0 (n=200)	99.2±14.4 (n=199)	99.0±16.0 (n=198)	65.5±13.1 (n=199)	0.6	<0.001	<0.001
CysC (mg/dL)	0.81±0.14 (n=198)	0.80±0.12 (n=180)	0.81±0.14 (n=198)	1.11±0.17 (n=199)	0.6	<0.001	<0.001
$eGFR_{cys}$ (mL/min/1.73m^2)	102.8±17.6 (n=198)	103.2±15.4 (n=180)	102.1±17.5 (n=198)	71.6±15.3 (n=199)	0.7	<0.001	<0.001
$eGFR_{cr\text{-}cys}$ (mL/min/1.73m^2)	102.0±16.3 (n=198)	102.0±13.9 (n=180)	101.3±16.8 (n=198)	67.4±11.6 (n=198)	0.8	<0.001	<0.001
Urea nitrogen (mg/dL)	14.3±3.8 (n=199)	14.0±3.3 (n=181)	14.5±4.0 (n=198)	18.0±4.4 (n=200)	0.2	<0.001	<0.001
UPCR (g/g)	61(50,114) (196)	66(50,128) (175)	62(50,128) (195)	70(50,116) (201)	0.3[a]	0.9[a]	0.5[a]
UACR (mg/g)	5.0(4.0,6.9) (186)	5.0(3.8,5.8) (167)	5.0(4.0,6.6) (193)	5.0(3.3,5.4) (198)	0.07[a]	0.1[a]	0.5[a]
Hemoglobin (g/dL)	13.6±1.2 (n=194)	13.6±1.2 (n=198)	13.6±1.4 (n=193)	13.1±1.2 (n=194)	0.9	<0.001	<0.001
Leukocyte count (/mm^3)	6.1±1.6 (n=195)	5.9±2.0 (n=198)	6.1±1.7 (n=193)	5.7±1.5 (n=194)	0.3	0.2	0.4
Serum albumin (mg/dL)	4.08±0.28 (n=199)	4.18±0.29 (n=199)	4.07±0.33 (n=198)	4.06±0.31 (n=200)	0.002	<0.001	<0.001
CRP (mg/dL)	1.1(0.5,2.7) (199)	0.9(0.4,1.7) (182)	1.4(0.6,3.1) (198)	1.2(0.7,2.9) (199)	0.1[a]	<0.001[a]	0.2[a]
Fibrinogen(mg/dL)	295±69 (n=197)	292±64 (n=181)	305±67 (n=198)	300±72 (n=198)	0.8	0.004	0.7
Homocysteine (mg/L)	1.20±0.35 (n=193)	1.22±0.39 (n=176)	1.20±0.34 (n=196)	1.49±0.43 (n=198)	0.8	<0.001	<0.001
Uric acid (mg/dL)	4.8±1.1 (n=200)	4.6±1.1 (n=198)	4.9±1.2 (n=198)	5.3±1.1 (n=200)	0.08	<.001	<.001
Serum calcium (mg/dL)	9.16±0.38 (n=200)	9.26±0.38 (n=199)	9.19±0.38 (n=198)	9.24±0.42 (n=200)	0.02	0.8	0.4
Serum phosphorus (mg/dL)	3.49±0.52 (n=198)	3.52±0.50 (n=199)	3.49±0.48 (n=198)	3.30±0.48 (n=200)	0.5	<0.001	<0.001
PTH (pg/mL)	42.8±16.3 (n=199)	42.3±17.8 (n=180)	42.8±15.6 (n=198)	52.7±20.9 (n=200)	0.6	<0.001	<0.001
Cholesterol (mg/dL)	186±37 (n=200)	185±35 (n=198)	186±36 (n=197)	186±35 (n=199)	0.7	0.7	0.6
LDL cholesterol (mg/dL)	112±33 (n=198)	110±31 (n=196)	111±30 (n=193)	110±31 (n=193)	0.6	0.7	0.6
HDL cholesterol (mg/dL)	55.2±16.5 (n=200)	56.2±14.5 (n=198)	54.9±16.4 (n=198)	54.1±13.9 (n=197)	0.5	0.002	0.03

Variable	Baseline Visit		6-Mo Visit		*P* [2]		
	Controls	Donors	Controls	Donors	Controls vs Donors [3]	Baseline vs 6 mo [4]	Interaction [5]
Triglycerides (mg/dL)	77 (55,113) (200)	76 (57,111) (198)	80 (59,119) (197)	84 (64,124) (199)	0.8[a]	<0.001[a]	0.05[a]
Lipoprotein(a) (mg/dL)	12.0(5,41) (199)	16.0(5,49) (181)	16.0(5,43) (198)	20(5,55) (200)	0.3[a]	0.003[a]	0.5[a]
Hemoglobin A1c (%)	5.3±0.34 (196)	5.2±0.32 (177)	5.3±0.36 (195)	5.3±0.31 (197)	0.03	<0.001	0.6
Glucose (mg/dL)	91.8±9.9 (200)	91.9±12.2 (198)	91.2±8.9 (197)	89.2±8.5 (199)	0.9	0.003	0.05
Insulin (pmol/L)	36(24,60.0) (191)	36(24,54) (176)	40(25,64) (192)	36(24,54) (198)	0.4[a]	0.01[a]	0.08[a]
HOMA IR	1.3(0.89,2.3) (191)	1.3(0.8,2.3) (175)	1.5(1.0,2.5) (191)	1.3(0.9,2.1) (197)	0.6[a]	0.04[a]	0.07[a]

Note: Values are given as mean ± standard deviation or median [interquartile range] (number sampled). Conversion factors for units: creatinine in mg/dL to μmol/L, x88.4; urea nitrogen in mg/dL to mmol/L, x0.357; fibrinogen in mg/dL to μmol/L, x0.0294; homocysteine in mg/L to μmol/L, x7.397; uric acid in mg/dL to μmol/L, x 59.48; calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.3229; cholesterol, LDL cholesterol, and HDL cholesterol in mg/dL to mmol/L, x0.02586; triglycerides in mg/dL to mmol/L, x0.01129; glucose in mg/dL to mmol/L, x0.05551.

Abbreviations and definitions: mGFR, measured glomerular filtration rate (by iohexol plasma clearance); $eGFR_{Cr}$, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation; $eGFR_{cys}$, glomerular filtration rate estimated by Chronic Kidney Disease Epidemiology Collaboration cystatin C equation; $eGFR_{Cr\text{-}cys}$, glomerular filtration rate estimated by by Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation; 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; UPCR, urine protein-creatinine ratio; UACR, urine albumin-creatinine ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine; CysC, cystatin C; CRP, C-reactive protein; PTH, parathyroid hormone;

[a] based on logartithmically transformed values.

[2] 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.

[3] Controls v. donors P-values test overall differences between donors and controls.

[4] Baseline v. 6 mo P-values test overall differences between baseline (pre-donation) and 6-month visits.

[5] Interaction P-values test the interaction between donors v. controls and baseline v. 6-month visits.