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Clinical and Kidney Structural Characteristics of Living Kidney Donors With Nephrolithiasis and Their Long-term Outcomes

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Background. Nephrolithiasis in living kidney donors is concerning due to the potential impact on long-term postdonation kidney function. **Methods.** We performed a cohort study of living kidney donors from 2 centers with a baseline computed tomography scan and implantation renal biopsy. Donors (>5 y since donation) completed a follow-up survey or underwent chart review to assess eGFR and incident hypertension. Stone formers were classified as symptomatic if they had a past symptomatic episode or asymptomatic if only incidental radiographic kidney stones were identified during donor evaluation. We compared baseline clinical, imaging, and biopsy characteristics by stone former status including review of metabolic evaluations in stone formers. Long-term risks of renal complications (low eGFR and hypertension) by stone former status were evaluated. **Results.** There were 12 symptomatic and 76 asymptomatic stone formers among 866 donors. Overall, baseline clinical characteristics and implantation biopsy findings were similar between stone formers and non-stone formers. After a median follow-up of 10 y, stone former status was not associated with eGFR <60 mL/min/1.73 m2, eGFR <45 mL/min/1.73 m^2, or hypertension. **Conclusions.** Both asymptomatic and symptomatic SF have favorable histology findings at baseline. Long-term kidney outcomes were favorable in select stone formers with no evident increased long-term risk for decreased kidney function or hypertension after donation.

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The incidence of symptomatic and asymptomatic kidney stone disease in the general population is on the rise.[1] Therefore, it is not surprising that as many as 13% of potential kidney donors have a history of symptomatic nephrolithiasis or asymptomatic kidney stones found incidentally on computed tomography (CT) scan during donor evaluation.[2] In the general population, nephrolithiasis is associated with significant long-term morbidity, including chronic kidney disease and hypertension.[3-5] Several risk factors have been

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described to associate with future chronic kidney disease, end-stage renal disease, and proteinuria post–living kidney donation including older age, higher body mass index (BMI), hypertension, and subsequent diagnosis of diabetes.[6] The growing need for kidney transplantation has motivated transplant centers to broaden acceptance criteria to include medically complex living donors including donors with history of nephrolithiasis.[7,8] Although transplant centers have developed specific acceptance criteria for many comorbid conditions, a broad range of criteria has been implemented for potential donors with nephrolithiasis.[9-12]

There are numerous guidelines for evaluating potential living kidney donors with nephrolithiasis.[11] These guidelines have evolved to allow potential donors with asymptomatic stones or a distant history of symptomatic kidney stones to donate as long as the stone burden is low and metabolic evaluation is unremarkable. Early postdonation reported outcomes are favorable, including a low rate of kidney stone recurrence.[13,14] However, many of these studies were limited by short-term follow-up and small sample size and did not address other important outcomes, including postdonation kidney function. The newly published large study deriving from the "Renal and Lung Living Donors Evaluation" study revealed encouraging data that donors with a history of nephrolithiasis had similar long-term outcomes when matched to non-stone formers. However, it lacked granular data on stone formers (SFs) (symptomatic versus asymptomatic), metabolic evaluation in SF, and other potential risk factors for stone recurrence.[15] This data would help guide clinicians in providing better risk assessments for donors with stones on potential long-term complications.

The Aging Kidney Anatomy study cohort has detailed biopsy characteristics of kidneys in living donors and their long-term outcomes.[16,17] This cohort offers a unique opportunity to study the clinical and structural characteristics of donors with nephrolithiasis and their long-term outcomes.

MATERIALS AND METHODS

Study Design and Population

This study was approved by the Mayo Clinic Institutional Review Board. The patients involved in our study provided written informed consent. We surveyed adult (≥18 y old) living kidney donors from the Aging Kidney Anatomy Study[16] at Mayo Clinic (Minnesota and Arizona) who underwent donor nephrectomy from May 1, 1999 to March 1, 2013 and who had at least 5 y of postdonation follow-up. Inclusion criteria were the availability of high-resolution CT scan images (obtained at the time of donor evaluation) and adequate renal implantation biopsy (with ≥2 mm^2 of nondistorted cortex with ≥4 glomeruli) obtained at the time of transplant surgery. The Mayo Clinic Survey Research Center contacted donors via mailed surveys and follow-up phone calls from April 1, 2017 to December 31, 2019, using Accurint (www.accurint.com) to update contact information. Donors were asked to complete the survey via mail or phone interview. We requested donors provide recent (within the past 2 y) blood pressure readings, height, weight, and serum creatinine levels, along with testing dates. We offered remuneration to those lacking a recent blood pressure, height, weight, or serum creatinine to obtain these tests from a local provider. Donors who did not complete the survey but had a clinical follow-up in the Mayo Clinic Health System had their latest serum creatinine along with available height, weight, and blood pressure measurements manually abstracted from their medical records. Length of follow-up was determined by date of kidney donation until the date of the latest GFR measurement.

Kidney Donors With Nephrolithiasis

All donors were assessed for personal history of nephrolithiasis (including the number of prior episodes and time since the last symptomatic episode) and the presence of asymptomatic nephrolithiasis on evaluation CT scan. Donors with nephrolithiasis, termed SFs, were classified as symptomatic SF if they had a prior clinical episode with or without nephrolithiasis on CT scan during donor evaluation and asymptomatic SF if no prior history of symptomatic stones but the presence of asymptomatic nephrolithiasis was incidentally found during kidney donor evaluation. Notably, none of the asymptomatic SFs had previously known asymptomatic nephrolithiasis on imaging before the donor evaluation. We described the stone burden by stone location, the number of stone(s) present on imaging, and the largest stone diameter. Donors who were not symptomatic SF or asymptomatic SF were termed non-SF.

Donors that were SFs were evaluated according to evolving national and international protocols and guidelines over time.[11] SFs were evaluated in conjunction with a nephrologist specializing in kidney stone disease. SFs underwent metabolic stone evaluation and in later years a 24 h urine collection for urine chemistries. SFs with a history of rare stone types (eg, cysteine, struvite), nephrocalcinosis, and underlying metabolic disorders, including distal renal tubular acidosis, primary hyperoxaluria, and enteric hyperoxaluria, were excluded from donation. Of note, regardless of stone history, all donors with a history of gastric bypass surgery also underwent 24 h urine evaluation for urine oxalate, and those with high oxalate (≥40 mg/24 h) were excluded. Potential relative contraindications to donation were abnormal metabolic evaluation (eg, hypercalciuria), markedly low 24 h urine volume (<1000 mL),

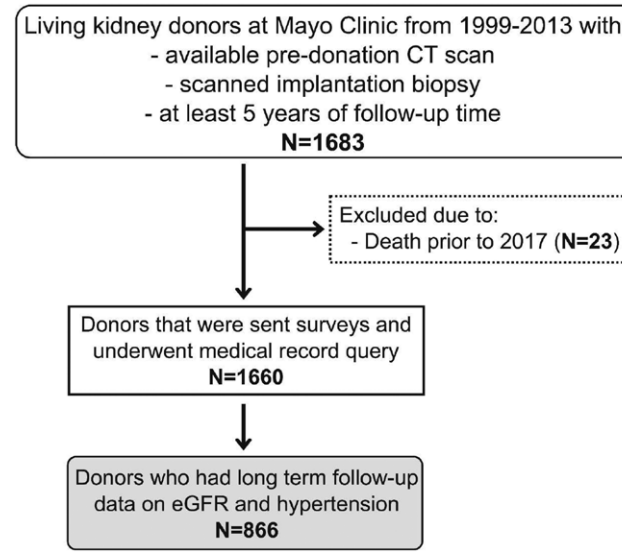

FIGURE 1. Selection of kidney donors with long-term follow-up.

TABLE 1.

Baseline clinical characteristics by kidney stone group

Clinical characteristics	Group 1: non-stone formers (N = 778), mean ± SD or N(%)	Group 2: asymptomatic stones only (N = 76), mean ± SD or N(%)	Group 3: symptomatic stone formers (N = 12), mean ± SD or N(%)	*P*, group 1 vs 2	*P*, group 1 vs 3
Age (y)	46.6 ± 11.9	45.6 ± 11.6	50.5 ± 10.4	0.29	0.26
Male	285 (36.6)	29 (38.2)	7 (58.3)	0.79	0.12
Caucasian	715 (91.9)	70 (92.1)	12 (100)	0.95	0.30
Predonation hypertension	92 (11.8)	15 (19.7)	2 (16.7)	0.05	0.64
Predonation SBP (mm Hg)	120.6 ± 14.9	121.8 ± 15.8	126.3 ± 11.3	0.87	0.82
Predonation DBP (mm Hg)	72.8 ± 9.5	74.5 ± 10.2	73.4 ± 10.7	0.30	0.55
Body mass index (kg/m^2)	27.8 ± 4.8	28.1 ± 6.0	30.5 ± 5.9	0.77	0.07
Obesity (BMI ≥ 30 kg/m^2)	232 (29.8)	23 (30.3)	6 (50)	0.94	0.11
Total cholesterol	196.2 ± 37.0	196.9 ± 36.4	190.4 ± 33.8	0.98	0.59
Triglycerides	114.6 ± 68.2	131.2 ± 105.2	157.7 ± 208.9	0.28	0.60
HDL cholesterol	59.0 ± 16.4	55.1 ± 14.8	54.5 ± 17.3	**0.04**	0.37
Fasting glucose	93.8 ± 8.6	93.8 ± 9.1	100.8 ± 19.4	0.91	0.31
Metabolic syndrome	122 (15.7)	18 (23.6)	4 (33.3)	0.07	0.71
Bariatric surgery	4 (0.5)	0	1 (8.3)	0.99	0.07
History of urinary tract infections	58 (6.8)	6 (7.9)	2 (16.7)	0.89	0.23
Thiazide diuretic	27 (3.5)	8 (10.5)	0	**0.003**	0.99
Vitamin C supplement	51 (6.6)	4 (5.3)	0	0.81	0.99
Calcium supplement	123 (15.8)	11 (14.5)	3 (25)	0.76	0.41
Serum calcium (mg/dL)	9.6 ± 0.3	9.5 ± 0.4	9.5 ± 0.37	0.20	0.83
Serum phosphorus (mg/dL)	3.6 ± 0.7	3.5 ± 0.6	3.5 ± 1.1	0.61	0.16
Serum uric acid (mg/dL)	5.1 ± 1.3	5.3 ± 1.5	5.3 ± 1.6	0.45	0.73
eGFR (mL/min/1.73 m^2)	87.8 ± 15.0	86.4 ± 14.0	81.3 ± 10.5	0.49	0.16
Measured GFR (mL/min/1.73 m^2)	101.5 ± 19.6	99.7 ± 16.7	95.1 ± 10.6	0.64	0.37
24 h urine albumin (mg)	4.6 ± 7.4	4.2 ± 4.6	4 ± 3.7	0.43	0.62
24 h urine total protein (mg)	258 (37.2)	52.7 (43.2)	58.3 ± 44.0	0.15	0.44
24 h urine volume (mL)	2149.8 ± 947.0	2159.1 ± 822.1	2264.3 ± 798.8	0.79	0.11
24 h urine volume <1000 mL	59 (9.3)	5 (6.6)	1 (8.3)	0.45	0.94
Donor nephrectomy—right	149 (19.2)	23 (30.3)	2 (16.7)	**0.02**	0.99

Bolded *P*-values - significant for $P < 0.05$.
BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure.

TABLE 2.

Baseline structural characteristics by kidney stone group

Structural characteristics, mean ± SD or n (%)	Group 1: non-stone formers (N = 778), mean ± SD or N(%)	Group 2: asymptomatic stones only (N = 76), mean ± SD or N(%)	Group 3: symptomatic stone formers (N = 12), mean ± SD or N(%)	*P*, group 1 vs 2	*P*, group 1 vs 3
Macrostructural characteristics					
Medullary sponge kidney	7 (0.9)	4 (5.3)	0	**0.01**	0.99
Focal scarring	13 (1.7)	3 (3.9)	0	0.16	0.99
Parenchymal thinning	1 (0.1)	1 (1.3)	0	0.17	0.99
Nephron size and number					
Glomerular volume (mm^3)	0.003 ± 0.001	0.003 ± 0.001	0.003 ±0.0006	0.73	0.96
Cortex volume per glomerulus (mm^3)	0.08 ± 0.04	0.07 ± 0.03	0.07 ± 0.03	0.95	0.72
Tubular cross-sectional area (μm^2)	4533 ± 1504	4332 ± 1626	4672.1 ± 1358.1	0.11	0.69
Nephron number per kidney	863 927 ± 383 690	811 576 ± 323 033	886 980.7 ± 478 924.3	0.44	0.86
Nephrosclerosis					
Globally sclerotic glomeruli (%)	3.5 ± 6.4	3.9 ± 6.6	2.9 ± 4.7	0.52	0.85
Number of IF/TA foci	0.5 ± 1.1	0.7 ± 1.4	0.2 ± 0.4	0.05	0.47
Range	0-10	0-6	0-1		
Percentage IF/TA by age				0.17	0.77
0%	589 (75.3)	52 (71.2)	10 (83.3)		
<1%	61 (7.8)	8 (10.9)	2 (16.7)		
1%–5%	104 (13.3)	10 (13.7)	0		
6%–10%	20 (2.6)	3 (4.1)	0		
>10%	8 (1.0)	0	0		
Artery luminal stenosis (%)	37.8 ± 12.5	38.1 ± 12.3	30.6 ± 8.9	0.79	**0.03**
Any arteriolar hyalinosis	7 (1.1)	2 (3.2)	0	0.19	0.99

Bolded *P*-values - significant for $P < 0.05$.
IF/TA, interstitial fibrosis/tubular atrophy.

TABLE 3.

Characteristics of stone disease in stone formers

Clinical characteristics of stone formers	Asymptomatic stones only (N = 76), mean ± SD or N (%)	Symptomatic stone formers (N = 12), mean ± SD or N (%)
Symptomatic stone history		
More than 1 prior symptomatic stone	N/A	4 (25%)
Time from last symptomatic stone to donation (y)	N/A	11.1 ± 5.5
Family history of stone disease	8 (10.5)	4 (33.3)
Characteristics of radiographic stones		
Number of stones	1.6 ± 1.7	0.42 ± 0.99
1 stone	58 (76.3)	0 (0)
2 stones	10 (13.2)	1 (8.3)
>2 stones	8 (10.5)	1 (8.3)
Range	1-12	0-3
Bilateral stones	11 (14.3)	2 (16.7)
Largest stone diameter	1.8 ± 1.3	3.5 ± 0.7
Stone laterality		
Right	34 (44.7)	0
Left	31 (40.8)	0
Bilateral	11 (14.3)	2 (13.6)
Location of stone(s)		
Lower pole	41 (53.9)	0
Middle pole	12 (15.8)	0
Upper pole	11 (14.5)	0
Multiple[a]	12 (15.8)	2 (16.7)
24 h urine supersaturation studies	39 (51.3)	8 (66.7)
Two supersaturation studies	17 (22.4)	2 (16.7)
Urine pH	6.1 ± 0.5	6.0 ± 0.6
Urine pH <5.5 or >6.5	24 (32.4)	4 (36.3)
CaOx supersaturation (DG)	1.0 ± 0.9	1.1 ± 0.9
CaOx supersaturation >1.77 (DG)	5 (15.6)	3 (37.5)
CaPhos supersaturation (DG)	3.4 ± 2.1	3.6 ± 2.0
CaPhos supersaturation >3.96 (DG)	11 (34.4)	4 (50.0)
Urine calcium (mg/24 h)	176.1 ± 81.2	196.4 ± 89.8
Urine calcium ≥200 mg/24 h	11 (28.2)	3 (37.5)
Urine sodium (mmol > 24h)	152.5 ± 65.5	155.6 ± 80.7
Urine sodium ≥200 mmol/24 h	11 (20.0)	3 (33.3)
Urine oxalate (mg/24 h)	24.7 ± 7.6	24.6 ± 7.3
Urine oxalate ≥40 mg/24 h	3 (8.1)	1 (12.5)
Urine citrate (mg/24 h)	702.1 ± 338.0	703.4 ± 262.2
Urine citrate ≤300 mg/24 h	6 (15.8)	1 (12.5)
Urine uric acid (mg/24 h)	591.5 ± 208.8	576.3 ± 215.1
Urine uric acid ≥700 mg/24 h	7 (21.9)	2 (25.0)
Any 24 h urine abnormality	35 (81.4)	7 (87.5)

[a]SF with multiple stones located in different regions of the kidney(s).
CaOx, calcium oxalate; CaPhos, calcium phosphate.

younger age (≤40 y old), significant stone burden on imaging including bilateral stone disease, and medullary sponge kidney (MSK). Favorable characteristics that contributed to the acceptance of symptomatic SF, particularly those with recurrent episodes, included: older age, longer time—at least 3 y—since last episode, no evidence of stone formation on serial imaging with prior CT scans were available for comparison), and normal or easily correctable 24 h urine chemistries. Select SF with an abnormal metabolic evaluation received treatment (including thiazide diuretics or citrate supplementation) and were approved to donate.[18] All SFs received dietary education to lower the risk of stone formation. SFs with asymptomatic kidney stone(s) typically donated a kidney with stone(s) to leave the donor with a stone-free kidney and reduce their risk of a stone event long-term. Although rare, accepted SFs with bilateral asymptomatic nephrolithiasis donated the stone-bearing kidney with larger/more stone(s). Deviations from this protocol occurred per surgeon discretion.

Available values, including urine calcium, sodium, oxalate, citrate, and uric acid, were manually abstracted from valid 24 h urine supersaturation studies based on urine creatinine (10–29 mg/kg) collected from SFs. If multiple 24 h urine studies were available, we reported the average values. Supersaturation for calcium oxalate and hydroxyapatite or calcium phosphate crystals were abstracted and calculated using EQUIL2.[19] We included the 24 h urine volume and urine pH from the standard donor evaluation 24 h urine protein study and urinalysis, respectively. Serum parathyroid hormone was obtained if parathyroid disease was suspected.

Donor Clinical Characteristics

Baseline data were obtained from the extensive evaluations of kidney donors before undergoing kidney donation as previously described.[16] The predonation evaluation included serum creatinine to estimate glomerular filtration rate (eGFR),[20] iothalamate clearance to measure GFR, 24 h urine albumin, BMI, office blood pressure, and CT scan imaging of the kidneys. Acceptance criteria for donation varied by site and era, but in general included 24 h urine albumin excretion <30 mg and a measured glomerular filtration rate (GFR) normal for age. Mild hypertension in older donors and moderate obesity (BMI 30–35 kg/m^2; occasionally up to 40 kg/m^2 in older donors) were allowed. Hypertension was defined as a preexisting diagnosis of hypertension, an office systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication(s) to treat hypertension. Acceptable predonation "mild" hypertension was defined by either office blood pressure of 140–159/90–99 mm Hg or controlled with 1 antihypertensive medication (with or without a thiazide diuretic). Of note, all thiazide diuretics at baseline were being used to treat hypertension before donation and not for stone prevention.

Microstructural and Macrostructural Characteristics of Donors

As part of routine clinical care, intraoperative needle core biopsy of the renal cortex was performed at the time of transplantation. The tissue specimen was fixed in formalin and embedded in paraffin. Two sections (2–3 μm thickness) from the biopsy core were stained, 1 with periodic acid–Schiff and 1 with Masson trichrome, and were subsequently scanned into high-resolution digital images (Aperio XT digital scanner; Leica Biosystems). Nephron size on biopsy was characterized by mean nonsclerotic glomerular volume, cortex volume per glomerulus (reciprocal of nonsclerotic glomerular volumetric density), and mean cross-sectional tubular area as previously described.[21] Nephrosclerosis on biopsy was characterized by the percentage of glomeruli that were globally sclerosed, the percentage of interstitial fibrosis/tubular atrophy of the cortex area, the number of distinct interstitial fibrosis/tubular atrophy foci, and the severity of arteriosclerosis.[21] The severity of arteriosclerosis was determined by the percentage of luminal stenosis due to intimal thickening in the small-medium artery (if any present) most orthogonal to its axis. These were performed by personnel unaware of the donors' characteristics and outcomes. The presence of any arteriolar hyalinosis required a

TABLE 4.

Long-term outcomes of asymptomatic stone formers vs non-stone formers

Outcomes, mean ± SD or n (%)	Group 1: non-stone formers (N = 778), mean ± SD or N (%)	Group 2: asymptomatic stones only (N = 76), mean ± SD or N (%)	Unadjusted model estimate	*P*	Adjusted[a] model estimate	*P*
Median follow-up (y)	9.9 (7.5-13.0)	9.6 (7.2-12.4)				
Follow-up eGFR (mL/min/1.73 m^2)	65.9 ± 16.0	66.4 ± 17.3				
Residual eGFR %	75.5 ± 15.8	77.0 ± 16.4	0.75 (–1.1 to 2.6)[b]	0.43	0.65 (–1.2 to 2.5)[b]	0.48
eGFR <60 mL/min/1.73 m^2	311 (40.0)	29 (38.2)	0.92 (0.57 to 1.5)[c]	0.76	1.02 (0.75 to 1.40)[c]	0.89
eGFR <45 mL/min/1.73 m^2	48 (6.2)	6 (7.9)	1.30 (0.54 to 3.15)[c]	0.56	1.45 (0.83 to 2.56)[c]	0.20
Incident hypertension	102 (13.1)	9 (11.8)	0.95 (0.49 to 1.85)[c]	0.87	1.02 (0.52 to 2.02)[c]	0.95

[a]Adjusted for age, sex, and follow-up time.
[b]Mean difference (95% CI).
[c]Odds ratio (95% CI).

TABLE 5.

Long-term outcomes of symptomatic stone formers vs non-stone formers

Outcomes, mean ± SD or n (%)	Group 1: non-stone formers (N = 778), mean ± SD or N (%)	Group 2: symptomatic stone formers (N = 12), mean ± SD or N (%)	Unadjusted model estimate	*P*	Adjusted[a] model estimate	*P*
Median follow-up (y)	9.9 (7.5-13.0)	9.7 (7.6-10.7)				
Follow-up eGFR (mL/min/1.73 m^2)	65.9 ± 16.0	69.2 (57.9-3.7)				
Residual eGFR %	75.5 ± 15.8	92.3 (64.8-103.4)	6.53 (2.0-11.1)[b]	**0.005**	7.18 (2.7-11.7)[b]	**0.002**
eGFR <60 mL/min/1.73 m^2	311 (40.0)	3 (25)	0.50 (0.13-1.86)[c]	0.30	0.34 (0.09-1.38)[c]	0.13
eGFR <45 mL/min/1.73 m^2	48 (6.2)	1 (8.3)	1.38 (0.17-10.93)[c]	0.76	1.08 (0.13-8.89)[c]	0.94
Incident hypertension	102 (13.1)	3 (25.0)	0.51 (0.07-3.97)[c]	0.52	0.51 (0.06-4.03)[c]	0.52

Bolded *P*-values - significant for $P < 0.05$.
[a]Adjusted for age, sex, and follow-up time.
[b]Mean difference (95% CI).
[c]Odds ratio (95% CI).

review of all 12 biopsy section slides by a pathologist to be detected (data only available for Mayo Clinic Minnesota).

Predonation CT images from the angiogram/cortical phase were downloaded onto a workstation for processing. The kidney cortical volumes were segmented using a semi-automated algorithm (ITK-SNAP software, version 2.2; University of Pennsylvania, Philadelphia, PA).[21] Nephron number per kidney was calculated from the product of cortical volume and nonsclerotic glomerular volumetric density as previously described.[22]

Donor Outcomes

Outcomes of donors were assessed by administered or mailed survey and medical record query of donors in the Mayo Clinic Health System for serum creatinine at least 5 y after donation. Kidney function at follow-up was calculated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation. Other kidney function outcomes included residual eGFR (follow-up eGFR/predonation eGFR × 100%), eGFR <60 mL/min/1.73 m^2, and eGFR <45 mL/min/1.73 m^2. Incident hypertension was assessed among those without predonation hypertension and defined by self-reported office systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or taking any new antihypertensive medication for the purpose to lower the blood pressure after donation. As reported previously, self-reported data have been validated when compared to objective in available medical records.[17,23] The survey was not designed to assess for stone recurrence and not all SFs had medical records for review, thus stone recurrence during follow-up was not assessed.

Statistical Analysis

Baseline clinical, microstructural, and macrostructural findings were reported as mean ± SD, or number (N) with percent (%.). Measures of nephrosclerosis and nephron number were dichotomized at the abnormal 95th (or fifth) percentiles for age as previously identified.[16] We assessed differences between non-SFs and SFs by parametric and nonparametric analysis. Clinical characteristics along with the presence or absence of stone disease were used as covariates in regression models to determine their association with long-term outcomes. Linear regression was used to predict follow-up eGFR and residual eGFR. Univariate and multivariable logistic regressions were used to predict eGFR <60, eGFR <45 mL/min/1.73 m^2, and incident hypertension at follow-up. Odds ratios were calculated for both unadjusted models and models adjusted for age, sex, and follow-up time. As a sensitivity analysis, non-SFs were matched separately to asymptomatic SFs (4:1 matched) and symptomatic SFs (2:1 matched) using a propensity score calculated from baseline clinical characteristics. Variables with missing values in the SFs were excluded from the propensity score. Long-term outcomes were then assessed with the same approach used for the unmatched analysis. Statistical analyses were performed using JMP software version 14.0.

RESULTS

Donor Clinical and Structural Characteristics

Among 1660 donors who met inclusion criteria and were alive at the time of survey evaluation, 866 donors had a

TABLE 6.

Propensity-matched clinical characteristics by kidney stone group

Clinical characteristics	Group 1: non-stone formers (N = 152), mean ± SD or N (%)	Group 2: asymptomatic stone formers (N = 76), mean ± SD or N (%)
Age (y)	45.5 ± 12.1	45.6 ± 11.6
Male	69 (45.4)	29 (38.2)
Caucasian	138 (90.8)	70 (92.1)
Predonation hypertension	26 (17.1)	15 (19.7)
Predonation SBP (mm Hg)	120.8 ± 14.9	121.8 ± 15.8
Predonation DBP (mm Hg)	74.3 ± 9.4	74.5 ± 10.2
Body mass index (kg/m^2)	27.9 ± 4.5	28.1 ± 6.0
Obesity (BMI ≥ 30 kg/m^2)	24 (50.0)	6 (50)
Total cholesterol[a]	194.8 ± 35.2	196.9 ± 36.4
Triglycerides[a]	120.1 ± 73.4	131.2 ± 105.2
HDL cholesterol[a]	56.6 ± 15.5	55.1 ± 14.8
Fasting glucose	93.5 ± 8.6	93.8 ± 9.1
Metabolic syndrome	32 (21.1)	18 (23.7)
Bariatric surgery	0 (0)	0 (0)
History of urinary tract infections	11 (7.2)	6 (7.9)
Thiazide diuretic	12 (7.9)	8 (10.5)
Vitamin C supplement	9 (5.9)	4 (5.3)
Calcium supplement	17 (11.2)	11 (14.5)
Serum calcium (mg/dL)	9.5 ± 0.3	9.5 ± 0.4
Serum phosphorus (mg/dL)	3.5 ± 0.8	3.5 ± 0.6
Serum uric acid (mg/dL)	5.4 ± 1.4	5.3 ± 1.5
eGFR (mL/min/1.73 m^2)	86.9 ± 15.6	86.4 ± 14.0
Measured GFR (mL/min/1.73 m^2)[a]	102.6 ± 21.4	99.8 ± 16.8
24h urine albumin (mg)[a]	5.0 ± 6.8	4.2 ± 4.6
24h urine total protein (mg)[a]	47.9 ± 29.1	52.7 ± 43.2
24h urine volume (mL)[a]	2273.1 ± 803.7	2159.1 ± 822.1
24h urine volume <1000 mL[a]	8 (5.3)	5 (6.6)
Donor nephrectomy – right	10 (20.8)	2 (16.7)

[a]Variables not used included in propensity matching due to missing data in the asymptomatic stone formers group.
Non-stone formers (N = 152) were matched 2:1 to asymptomatic stone formers (N = 76) using a propensity score calculated from these baseline clinical characteristics.
BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure.

TABLE 7.

Propensity-matched clinical characteristics by kidney stone group

Clinical characteristics	Group 1: non-stone formers (N = 48), mean ± SD or N (%)	Group 3: symptomatic stone formers (N = 12), mean ± SD or N (%)
Age (y)	48.1 ± *9.9*	50.5 ± 10.4
Male	24 (50.0)	7 (58.3)
Caucasian	48 (100)	12 (100)
Predonation hypertension	5 (10.4)	2 (16.7)
Predonation SBP (mm Hg)	121.9 ± 14.2	126.3 ± 11.3
Predonation DBP (mm Hg)	74.5 ± 9.4	73.4 ± 10.7
Body mass index (kg/m^2)	30.0 ± 5.0	30.5 ± 5.9
Obesity (BMI ≥ 30 kg/m^2)	24 (50.0)	6 (50)
Total cholesterol	192.5 ± 32.0	190.4 ± 33.8
Triglycerides	139.3 ± 84.8	157.7 ± 208.9
HDL cholesterol	55.2 ± 16.8	54.5 ± 17.3
Fasting glucose	101.5 ± 12.0	100.8 ± 19.4
Metabolic syndrome	15 (31.2)	4 (33.3)
Bariatric surgery	0 (0)	1 (8.3)
History of urinary tract infections	8 (16.7)	2 (16.7)
Thiazide diuretic	0 (0)	0 (0)
Vitamin C supplement	0 (0)	0 (0)
Calcium supplement	9 (18.8)	3 (25.0)
Serum calcium (mg/dL)	9.5 ± 0.3	9.5 ± 0.4
Serum phosphorus (mg/dL)	3.5 ± 0.5	3.5 ± 1.1
Serum uric acid (mg/dL)	4.8 ± 1.2	5.3 ± 1.6
eGFR (mL/min/1.73 m^2)	85.3 ± 15.1	81.3 ± 10.5
Measured GFR (mL/min/1.73 m^2)[a]	100.8 ± 19.4	95.1 ± 10.7
24h urine albumin (mg)[a]	4.9 ± 7.4	4.0 ± 3.7
24h urine total protein (mg)	54.2 ± 33.4	58.3 ± 44.0
24h urine volume (mL)[a]	2033.3 ± 814.6	2264.3 ± 798.8
24h urine volume <1000 mL[a]	6 (12.5)	1 (8.3)
Donor nephrectomy – right	10 (20.8)	2 (16.7)

[a]Variables not used included in propensity matching due to missing data in the symptomatic stone formers group. SBP, systolic blood pressure.
Non-stone formers (N = 48) were matched 4:1 to symptomatic stone formers (N = 12) using a propensity score calculated from baseline clinical characteristics.
BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein.

long-term follow-up serum creatinine (**Figure 1**). There were 778 non-SFs, 76 asymptomatic SFs, and 12 symptomatic SFs. Nearly all baseline clinical characteristics were similar (**Table 1**). Asymptomatic SFs were more likely to take a thiazide diuretic for the treatment of hypertension. Symptomatic SF had less artery luminal stenosis. Nearly all baseline structural characteristics were also similar (**Table 2**). Non-SFs were less likely to have MSK than asymptomatic SFs.

Characteristics of Stone Disease Among SFs

Symptomatic SFs reported a mean 1.4 ± 0.7 prior symptomatic (range 1–3) episodes, with 4 (25%) reporting at ≥2 episodes. One donor required shockwave lithotripsy to facilitate stone passage while the remaining donors passed stone(s) spontaneously. The mean time from the last symptomatic stone event to kidney donation was 11.1 ± 5.5 (range 3–20) y. Family history of kidney stone disease among all SF was 13.6%. Two symptomatic SFs had bilateral kidney stones, whereas the remaining symptomatic SFs were stone-free (**Table 3**). The mean number of stones was 1.6 ± 1.7 (range 1–12) in asymptomatic SFs and 0.42 ± 0.99 (range 0–3) in symptomatic SFs. The asymptomatic SFs with 12 stones had only very small (<1 mm) bilateral calcifications in the setting of MSK of unclear significance. The lower pole was the most common location for stone(s) in asymptomatic SFs. Two SFs received targeted medical therapy for stone prevention before donation. The stone composition was known in 4 symptomatic SFs, and all were primarily calcium-based. Urine pH was <5.5 or >6.5 in 32.9% of SF. Over half (53.4%) of SFs had at least 1 valid 24 h urine SS study for evaluation. The most common abnormalities were elevated calcium phosphate SS (37.5%), hypercalciuria (29.8%), hyperuricosuria (22.5%), elevated urine sodium (21.9%), and hypocitraturia (15.2%). One donor received hydrochlorothiazide for hypercalciuria and 1 donor received potassium citrate for hypocitraturia with normalization of these parameters before donation.

Stone Characteristics at Time of Donation

At the time of kidney donation, asymptomatic SFs were more likely to undergo right nephrectomy than non-SFs

TABLE 8.

Long-term outcomes in asymptomatic stone formers and propensity-matched non-stone formers (as shown in Table 6)

Outcomes	Group 1: non-stone formers (N = 152), mean ± SD or N (%)	Group 2: asymptomatic stone formers (N = 76), mean ± SD or N (%)	Unadjusted model estimate	*P*	Adjusted[a] model estimate	*P*
Follow-up (y), median (IQR)	10.5 (8.3-13.4)	9.6 (7.2-12.4)				
Follow-up eGFR (mL/min/1.73 m^2)	65.5 ± 16.1	66.4 ± 17.3				
Residual eGFR %	76.4 ± 17.9	77.0 ± 16.4	0.66 (–4.14 to 5.46)[b]	0.791	1.56 (–3.22 to 6.32)[b]	0.523
eGFR <60 mL/min/1.73 m^2	62 (40.8)	29 (38.2)	0.90 (0.51 to 1.58)[c]	0.702	0.86 (0.46 to 1.59)[c]	0.624
eGFR <45 mL/min/1.73 m^2	13 (8.6)	6 (7.9)	0.92 (0.33 to 2.51)[c]	0.865	0.79 (0.27 to 2.27)[c]	0.658
Incident hypertension	14 (9.2)	9 (11.8)	1.32 (0.55 to 3.21)[c]	0.535	1.29 (0.52 to 3.20)[c]	0.576

[a]Adjusted for age, sex, and follow-up time.
[b]Mean difference (95% CI).
[c]Odds ratio (95% CI).

TABLE 9.

Long-term outcomes in symptomatic stone formers and propensity-matched non-stone formers (as shown in Table 7)

Outcomes	Group 1: non-stone formers (N = 48), mean ± SD or N (%)	Group 3: symptomatic stone formers (N = 12), mean ± SD or N (%)	Unadjusted model estimate	*P*	Adjusted[a] model estimate	*P*
Follow-up (y), median (IQR)	9.9 (8.4-12.1)	9.7 (8.2-10.4)				
Follow-up eGFR (mL/min/1.73 m^2)	66.4 ± 15.6	70.2 ± 16.4				
Residual eGFR %	78.9 ± 17.8	88.6 ± 28.3	9.65 (–3.16 to 22.45)[b]	0.145	10.17 (–2.91 to 23.25)[b]	0.133
eGFR <60 mL/min/1.73 m^2	20 (41.7)	3 (25.0)	0.47 (0.11 to 1.94)[c]	0.295	0.32 (0.07 to 1.53)[c]	0.155
eGFR <45 mL/min/1.73 m^2	2 (4.2)	1 (8.3)	2.09 (0.17 to 25.2)[c]	0.561	1.49 (0.10 to 21.10)[c]	0.770
Incident hypertension	7 (14.6)	3 (25.0)	1.95 (0.42 to 9.04)[c]	0.392	2.20 (0.42 to 11.38)[c]	0.348

[a]Adjusted for age, sex, and follow-up time.
[b]Mean difference (95% CI).
[c]Odds ratio (95% CI).

(30.3% versus 19.2%, $P = 0.02$). Overall, 61 of 78 (78%) SFs with a stone on donor CT (76 asymptomatic SFs and 2 symptomatic SFs) donated a kidney containing stone(s). Therefore, 13 SFs that had bilateral stones at baseline and 17 additional asymptomatic SF were left with a kidney containing stone(s).

Long-term Outcomes of Living Kidney Donors

Over a median follow-up of 9.9 (7.5-12.9) y, no donors reached end-stage renal disease (whether requiring dialysis or kidney transplantation). The mean follow-up eGFR was 66.0 ± 16.1 mL/min/1.73 m^2, residual eGFR was 75.8%, 55 (6.4%) donors had eGFR <45 mL/min/1.73 m^2, 523 (60.3%) donors had eGFR <60 mL/min/1.73 m^2, and 114 (13.1%) developed incident hypertension.

When compared with non-SFs, asymptomatic SFs had similar long-term outcomes including residual eGFR, eGFR <60 mL/min/1.73 m^2, eGFR <45 mL/min/1.73 m^2, and incident hypertension in unadjusted and adjusted analysis (**Table 4**). Symptomatic SFs had a higher residual eGFR than non-SFs in both unadjusted ($P = 0.005$) and unadjusted analysis ($P = 0.002$) (**Table 5**). There was otherwise no association between symptomatic SFs and eGFR <60 mL/min/1.73 m^2, eGFR <45 mL/min/1.73 m^2, or incident hypertension.

As a sensitivity analysis, SFs were matched to non-SFs with a propensity score based on baseline characteristics (Tables 6 and 7). After propensity matching, risk of CKD outcomes did not differ between asymptomatic SFs and non-SFs (Table 8) or between symptomatic SFs and non-SFs (Table 9).

DISCUSSION

In this study, we found that the postdonation renal outcomes of SFs as compared with non-SFs were similar. Moreover, SFs and non-SFs had similar GFR at baseline as well as microstructural findings on the implantation biopsy. Abnormal 24 h urine studies were common in SFs. At a median follow-up of 10 y, all outcomes including eGFR and incident hypertension were similar. SFs were not at increased risk for reduced GFR or incident hypertension when compared to non-SFs.

In previous studies of 1957 potential donors at Mayo Clinic, nephrolithiasis was the most common nonvascular anatomical variation or abnormality on CT scan.[2,18] In those studies, the baseline clinical characteristics were similar between potential non-SFs and asymptomatic SFs; however, symptomatic SF were more likely to be older, be hypertensive, and have higher albuminuria. The SFs overall had lower urine volume and more macrostructural abnormalities, including MSK, parenchymal thinning, and focal scarring.[2] In our study, which included only approved donors, many of these findings were similar between groups, although asymptomatic SFs were more likely to take a thiazide diuretic for hypertension. It is likely potential donors with more significant abnormalities were excluded from donation including those with albuminuria.

Nearly all structural characteristics on the implantation renal biopsy were similar between non-SFs and SFs in this study. MSK was more common in asymptomatic SFs; however, the overall prevalence was low. Although MSK is associated with kidney stone formation, MSK is often diagnosed during the donor evaluation, even in the absence of stone formation

and with a normal metabolic evaluation.[24] Carefully selected donors with MSK have excellent long-term outcomes, especially when compared with nondonors with MSK.[24]

In our study, we did not find an association with any manifestation of kidney stone disease and postdonation reduced GFR in the intermediate to long term. This finding is somewhat unexpected given previous studies in the general population that have shown an association between nephrolithiasis and subsequent chronic kidney disease and end-stage renal disease.[3,5,25,26] However, our findings are similar to a recent large study that showed that selected donors with a history of kidney stones had similar long-term outcomes to a matched cohort.[27] There are many plausible explanations for these findings. Not all SFs are permitted to donate, and thus, the donor evaluation may successfully exclude higher risk SFs for CKD from donation. Although comorbidities including predonation hypertension, obesity, and metabolic syndrome were relatively common at baseline in this study, these findings were either mild or well-controlled and ultimately did not exclude donors from donating a kidney.

In this study, we found a higher residual eGFR among symptomatic SFs. The explanation for this finding is unclear, but it is possible a symptomatic SF has a high propensity to develop glomerular hyperfiltration after donation. Even so, hyperfiltration after donation is not clearly harmful.[28] Although we did not assess split renal function at baseline and could not confirm which kidney was affected by prior stone event(s) in all symptomatic SFs, they may have donated a kidney with lower contribution to the predonation GFR. Alternatively, there may be more selection toward health in selection of donors with a history of symptomatic stones, which is further supported by the less severe arteriosclerosis on biopsy (lower % artery luminal stenosis).

Although the overall stone burden in SFs was low, select SFs with multiple prior symptomatic stone events, bilateral stone disease, and MSK were allowed to donate. Abnormal 24 h urine chemistries were common among SFs that underwent 24 h urine evaluation before donation, similar to previously published literature.[14] Published guidelines recommend against donation if these findings are present during the donor evaluation.[11] The latter recommendation of a normal metabolic evaluation is not in keeping with prior literature that has shown that 24 h urine studies do not reliably predict recurrence.[29] However, all SFs in our study received education regarding dietary interventions and increasing urinary volume, which have been shown to reduce future risk of stone events.

This study has many strengths with findings that have not been previously described, including a long-term follow-up study of well-described symptomatic and asymptomatic SFs. We included comprehensive stone histories and metabolic evaluations as well as extensive comparisons of clinical, structural, and histologic data with non-SFs. In particular, we found that baseline histology was similar and favorable between SFs and non-SFs, which may help to explain comparable GFR long-term. We do acknowledge several limitations including a predominantly Caucasian donor population and lack of data on kidney stone recurrence. The sample of symptomatic SFs was relatively small and heterogeneous, which makes generalizability difficult. Nevertheless, few prior studies have compared this group of SFs with non-SFs and their outcomes overall were favorable. Although a median follow-up of 10 y may be insufficient to detect donors reaching end-stage renal disease, this study includes some of the longest follow-up of donors with history of kidney stones and provides encouraging data that the incidence of lower GFR was modest and similar between groups. Our study was not designed to assess stone recurrence. Other studies have suggested that recurrence of stone events is low even in the intermediate to long-term postdonation.[14,30] Although not all SF underwent a metabolic evaluation, this deficiency is seen in prior studies, and recommendations for obtaining 24 h urine studies have evolved over time.[11,14]

In conclusion, long-term renal outcomes between SF and non-SF living kidney donors are similar. SFs with a low stone burden at baseline and symptomatic SFs with a remote history of their past symptomatic stone events are at low risk for decreased GFR or incident hypertension. We recommend a thorough evaluation of kidney stone risk factors coupled with collaboration between the transplant providers and a nephrologist specializing in stone disease when available to provide a more thorough risk assessment for kidney stone recurrence. Interventions to reduce stone risk are also indicated.

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