HHS Public Access

Author manuscript

Mayo Clin Proc. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Mayo Clin Proc. 2016 December ; 91(12): 1744–1752. doi:10.1016/j.mayocp.2016.08.014.

Kidney Function After the First Kidney Stone Event

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Abstract

Objective—To determine if there is a persistent decline in kidney function after the first kidney stone event.

Patient and Methods—Incident symptomatic stone formers and age- and sex-matched controls underwent 2 study visits 90 days apart to assess kidney function, complete a survey, and have their medical records reviewed. Kidney function was compared between stone formers and controls adjusting for clinical, blood, and urine risk factors.

Results—There were 384 stone formers and 457 controls. At visit 1, a median of 104 days after the stone event, stone formers compared with controls had similar serum creatinine (0.86 vs 0.84 mg/dL; P=.23), higher serum cystatin C (0.83 vs 0.72 mg/L; P<.001), higher urine protein (34.2 vs

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19.7 mg/24 h; *P*<.001) levels, and were more likely to have albuminuria (24 h urine albumin >30 mg: 5.4% vs 2.2%; *P*=.02). Findings were similar after adjustment for risk factors and at visit 2, a median of 92 days after visit 1. In the 173 stone formers with serum creatinine levels from care before study participation, the mean serum creatinine level was 0.84 mg/dL before the stone event, increased to 0.97 mg/dL (*P*<.001) at the stone event, but returned to 0.85 mg/dL (*P*=.38) after the stone event (visit 1).

Conclusions—Incident symptomatic stone formers have a rise in serum creatinine levels that resolves. However, stone formers have sustained higher cystatin C levels and proteinuria that may affect long-term risk of chronic kidney disease.

Keywords

kidney calculi; nephrolithiasis; chronic kidney disease; kidney function; proteinuria

INTRODUCTION

Kidney stones are an increasingly prevalent peril afflicting 7.2 to 7.7% of the adult population.[1,2] An increased risk of chronic kidney disease (CKD) and kidney failure with kidney stones has been previously shown in most[2–6] but not all[7] population-based cohort studies. Links observed between kidney stones and vascular risk factors such as hypertension, hyperlipidemia, metabolic syndrome, diabetes mellitus, and obesity have suggested the possibility of shared pathophysiology contributing to this risk of CKD,[8,9] but the increased risk of CKD with kidney stones has not been explained in analyses that account for these risk factors. Other risk factors such as 24h urine chemistries, environmental exposures, and genetic factors may be responsible for an increased risk of CKD in stone formers and have not been accounted for in prior analyses.

A clearer understanding of the risk for CKD among stone formers also requires better validation and characterization of both stone disease and kidney function. Reliance on diagnostic codes or surveys to identify symptomatic stone formers lacks confirmation that there was ever an actual stone that passed through the ureter. Asymptomatic and incidental kidney stones are common[10] and may be disproportionately detected in patients who have frequent radiographic studies for other conditions associated with CKD. Alternatively, suspected stone formers without a stone confirmed by imaging or patient collection may have other predispositions for CKD (e.g., chronic analgesic use for back pain or unrecognized renal tumors). Studies focused on prevalent stone formers rather than incident stone formers are likely enriched for patients with multiple recurrent stone events. Many incident stone formers actually have a low risk of recurrence,[11] but if the first stone event is associated with CKD, monitoring kidney function may be important. Finally, reliance on clinically obtained data to detect CKD among stone formers is a limitation of prior studies because kidney function testing occurs more often in stone formers than non-stone formers and may lead to a detection bias.[3]

To address these limitations, this prospective study compared kidney function between validated incident symptomatic stone formers and controls in the community who completed two study visits 90 days apart. Detailed risk factors, stone disease characteristics, and kidney

function tests were captured by surveys, chart review, blood chemistries, and 24-h urine chemistries at the study visits.

METHODS

Study population

Continuous surveillance of clinical databases for kidney stone diagnostic codes and the term "kidney stone" (or a synonym) in clinical notes was used to identify and recruit incident adult stone formers in Minnesota and Florida. Inclusion criteria were a recent first-time symptomatic stone event (obstructing or passed stone with pain and/or gross hematuria) confirmed by both participant interview and manual chart review. Controls were recruited using local mailings and community flyers. Control recruitment was frequency-matched on age and sex to the stone former cohort. Recruited stone formers and controls at the Minnesota site had to live within Olmsted County or an adjacent county and were identified using the resources of the Rochester Epidemiology Project.[12] Stone formers had to receive care from an Olmsted County provider for their first stone event. Recruited stone formers and controls at the Florida site had to live within 100 miles of Mayo Clinic Florida and the stone formers had to receive care for their first stone event at Mayo Clinic Florida. All participants were adults (age ≥18 years) who could complete a survey and study visit on their own. These incident symptomatic stone formers and controls were recruited from Minnesota between 1/1/2009 and 1/16/2015 and from Florida between 1/1/2011 and 1/16/2015. Stone formers and controls with chronic kidney disease based on either chart review or an $eGFR_{Cr}$ (CKD-EPI creatinine-based estimated glomerular filtration rate)[13] <60 ml/min/1.73 m^2 prior to their stone event for stone formers or study participation for controls were excluded.

Study visits

Participants underwent two study visits. For stone formers, visit 1 occurred after the symptomatic stone had fully resolved (passed or surgically removed). Visit 1 included a fasting blood draw and a 24-h urine collection completed on the morning of their study visit. Blood pressure, height, and weight were also measured. Participants completed an administered survey on risk factors and co-morbidities; stone formers received an additional set of questions specific to stone disease. Visit 2 only involved a fasting blood draw and a 24-hour urine collection and was targeted to be 90 days after Visit 1.

Kidney function

Kidney function was assessed at visit 1 and visit 2 with serum creatinine (standardized isotope dilution mass spectrometry traceable enzymatic assay, Roche, Indianapolis, IN), serum cystatin C (particle enhanced turbidimetric assay, Gentian AS, Moss, Norway), 24-h urine protein (pyrogallol red colorimetric assay, Wako Diagnostics, Richmond, Virginia), and 24-h urine albumin (immunoturbidometric assay, Roche). Due to a large proportion of low urine albumin concentrations (≤5 mg/L), urine albumin was dichotomized as >5 mg versus ≤5 mg per 24-h or as >30 versus ≤30 mg per 24-h. Chronic kidney disease was identified by a 24-h urine albumin >30 mg or $eGFR_{Cr}$ <60 ml/min/1.73 m^2.[13] Any serum creatinine level obtained as part of clinical care during the 3 years prior to study

participation was identified. In addition, any serum creatinine level obtained during the symptomatic stone event was identified.

Other risk factors for kidney stones or chronic kidney disease

Clinical risk factors assessed by both survey and chart review included hypertension, diabetes, gout, history of urinary tract infection (UTI), diarrhea or loose stools, gastric bypass surgery, use of calcium supplements, and family history of stones. A history of working in hot temperatures and heat cramps were assessed by survey only. Laboratory measurements included serum bicarbonate, calcium, phosphate, and uric acid; and 24-h urine volume, calcium, chloride, citrate, magnesium, oxalate, phosphate, potassium, sodium, uric acid, creatinine, and pH (obtained at visit 1).

Statistical analysis

Clinical and laboratory characteristics at visit 1 were compared between stone formers and controls using linear and logistic regression models with adjustment for age and sex. Kidney function by serum creatinine, cystatin C, 24-h urine protein, and 24-h urine albumin was compared between stone formers and controls at both visit 1 and visit 2 using age-sex-adjusted and multivariable-adjusted linear and logistic regression models. The interaction of other risk factors on the association of kidney function with stone formers versus controls was also evaluated with regression models. Association of stone disease characteristics with each of the kidney function markers was assessed among stone formers using the equal variance t-test and Kruskal-Wallis test for continuous measurements and the chi-square test for dichotomized measurements. We required the urine creatinine to be between 400 mg and 3000 mg for the 24-h urine results to be usable in the analysis. A sensitivity analysis was performed in which only stone formers who had visit 1 between 3 weeks and 4 ½ months after the stone event and who had visit 2 between 4 ½ months and 1 year after the stone event were included for analysis. Among subjects with prior serum creatinine levels for clinical care (including the stone event), the trend in serum creatinine was assessed using paired t-tests.

RESULTS

Study sample and follow-up

There were 393 validated first-time symptomatic stone formers and 465 controls that were recruited and completed study visit 1. Stone formers that participated were more likely to have a family history of kidney stones and have had kidney stone surgery (Supplemental Table 1). None of the stone formers had kidney stones secondary to a metabolic disease (e.g. primary hyperparathyroidism). Those with CKD prior to their first stone event for stone formers or study enrollment for controls (9 stone formers and 8 controls, P=.55) were excluded, leaving 384 stone formers and 457 controls for analysis in this study (Figure 1). Visit 1 was a median (25^{th}%, 75^{th}%) 104 (58, 314) days after the stone event among stone formers. There were 293 stone formers and 409 controls that completed visit 2. Visit 2 was a median (25^{th}%, 75^{th}%) 92 (91, 99) days after Visit 1 among stone formers and 92 (91, 98) days after visit 2 among controls.

Comparison of stone formers to controls

Table 1 compares clinical characteristics between stone formers and controls with adjustment for age and sex. Stone formers were more likely to be obese and have a history of hypertension, prior urinary tract infections, diarrhea/loose stools, working in hot temperatures, heat cramps, calcium supplement use, and family history of kidney stones compared to controls ($p<0.05$ for all). Table 2 compares the serum and urine chemistries between stone formers and controls with adjustment for age and sex. Stone formers had higher levels of serum calcium, and uric acid than controls, as well as higher levels of urine calcium, phosphate, and creatinine. Meanwhile, levels of urine oxalate and potassium were lower in stone formers compared to controls. Urine creatinine is a marker of collection adequacy, but is also influenced by conditions that affect muscle mass such as obesity. After further adjusting for body mass index, differences in urine creatinine between stone formers and controls were no longer statistically significant ($P=.10$).

Kidney function at study visits

Table 3 compares kidney function in stone formers and controls at visits 1 and 2, with adjustment for age and sex as well as additional multivariable adjustment for all the characteristics in Tables 1 and 2. Stone formers had higher serum cystatin C and 24-hour urine protein levels at visits 1 and 2 compared with controls. Cystatin C levels remained higher in stone formers after multivariable adjustment at visits 1 and 2; 24-hour urine protein levels remained statistically significant after multivariable adjustment at visit 1 but was attenuated at visit 2. Stone formers were also more likely than controls to have urine albumin levels greater than 5 mg at visit 1, even after multivariable adjustment; however, this finding was also seen at visit 2, but was not statistically significant after multivariable adjustment. Approximately twice as many stone formers as controls had urine albumin levels greater than 30 mg or an $eGFR_{Cr}$ level less than $60mL/min/1.73m^2$ at visit 1 and visit 2.

Effect modification by other risk factors

Statistical interactions between each risk factor and stone former status were assessed for each kidney function measure (Supplemental Table 2). While there were a few statistically significant interactions between risk factors and kidney function markers, these interactions lacked consistency across different kidney function markers.

Stone disease characteristics and their association with kidney function

Supplemental Table 3 compares kidney function with specific characteristics of stone formers. Stone composition was available in 199 of 384 stone formers (52%). Significant differences were found across stone compositions in serum creatinine and urine albumin with uric acid stones having the most elevated levels. Other associations were not seen consistently across more than one kidney function marker.

Sensitivity Analyses

Since stone former and controls had similar racial distributions as well as age and sex matching, findings were not different using creatinine- or cystatin C-based eGFR rather than

serum creatinine or cystatin C (not shown). There were 226 stone formers who had visit 1 between 3 weeks and 4 ½ months after the stone event and 143 stone formers who had visit 2 between 4 ½ months and 1 year after the stone event. The kidney function findings in stone formers versus controls were substantively similar in this sensitivity analysis (Supplemental Table 4).

Trend in serum creatinine prior to study participation

Study enrollment occurred after the 1st stone event. Thus, we relied on past clinical data to assess the trend in serum creatinine before and after the stone event. Among the 384 first-time stone formers and 457 controls, 173 stone formers and 193 controls had a serum creatinine level prior to the stone event or visit 1 and their mean levels did not differ (0.84 vs 0.86 mg/dl, P=.77). The past serum creatinine levels in stone formers were obtained a median 202 days before the stone event. Among these stone formers, the mean serum creatinine increased at the stone event (0.84 mg/dl to 0.97 mg/dl, P<.001) but improved by visit 1 (0.84 mg/dL to 0.85 mg/dl, P=.38). Among controls with past serum creatinine levels, the mean serum creatinine levels prior to study participation were similar to those at visit 1 (0.86 mg to 0.87 mg/dl, P=.50) (Figure 2).

DISCUSSION

In this population-based prospective study we assessed kidney function after the first symptomatic stone event compared with controls. We found that there was a rise in serum creatinine levels at the time of the stone event, but this effect was transient and resolved by the first visit. We did observe persistently higher serum cystatin C and proteinuria levels in stone formers compared with controls. Thus, immediately after the first stone event, incident stone formers exhibit a kidney function marker pattern that is concerning for an increased risk of long-term adverse events such as end-stage renal disease.

Serum cystatin C levels were persistently higher in stone formers compared with controls, and serum creatinine levels were only transiently higher at the time of the stone event. A problem with serum creatinine and cystatin C is that both reflect non-GFR biology, even after use in eGFR equations.[14] The use of eGFR implicitly assumes that associations are due to the marker reflecting GFR. Instead, there are 2 plausible interpretations of these findings. First, it could be that stone disease is associated with higher cystatin C levels because cystatin C is detecting a reduction in GFR not detected by serum creatinine. Second, it could be that stone disease is associated with higher cystatin C levels because cystatin C is detecting non-GFR biology, such as inflammation, not detected by serum creatinine.[15] Regardless of which hypothesis is correct, a higher cystatin C level is still an adverse prognostic marker for end-stage renal disease and mortality.[16] We also found evidence of a sustained elevation in urine protein excretion in stone formers. The nature and cause of this proteinuria in incident stone formers deserves further study because it may contribute to the stone disease itself, the CKD risk, or both.

Prior cohort studies with long-term follow-up have found about a two-fold higher risk of CKD or end-stage renal disease in stone formers.[2–6] These studies have demonstrated that the increased risk of CKD in stone formers was independent of many traditional risk factors

that are common in stone formers including hypertension, diabetes, obesity, and gout. We also found these risk factors to be more prevalent in stone formers than controls. However, unlike prior studies we were able to adjust for numerous other risk factors that also tend to be enriched in stone formers, including a history of urinary tract infection, diarrhea, hot work environment, heat cramps, calcium supplement use, family history of kidney stones, serum calcium, serum phosphate, serum uric acid, urine calcium, urine phosphate, and urine creatinine. We found urine oxalate and urine potassium were lower in stone formers compared to controls. This may be due to diet preferences of stone formers being lower in vegetables that are enriched with oxalate and potassium. After adjusting for all these risk factors, we still found stone formers to have lower kidney function than controls. This study provides further evidence that the increased risk of CKD in stone formers is not simply explained by shared risk factors.

Our results showed that uric acid stone composition trended toward higher serum creatinine, cystatin C, and detectable albuminuria. This may be due to the older age of stone formers who present with uric acid stones compared to other stone types.[17] It is worth noting, however, that prior studies have suggested that uric acid stones are disproportionately associated with abnormal kidney function or CKD.[2,18–20] In a recent study, uric acid stones were associated with more collecting duct plugs than calcium oxalate stones and collecting duct plugs may contribute to kidney dysfunction.[21] Other investigators have related higher radiographic stone burden to decreased kidney function among patients undergoing shockwave lithotripsy.[22] We also found evidence that higher urine sodium was synergistic for increasing the association between kidney stone and albuminuria. Urine sodium is reflective of dietary sodium and higher dietary sodium intake increases intraglomerular pressure leading to proteinuria.[23] Lower sodium intake is already advised to prevent stone recurrence,[24] but may also have benefits in decreasing the risk of proteinuria in stone formers. We found no evidence that more radiographic stone burden (size or number) associated with decreased kidney function among incident stone formers.

There are several potential mechanisms for the early loss of kidney function after the first stone event. It has been hypothesized that transient renal obstruction during stone passage and damage from procedures may result in nephron damage.[4,25] However, we found no evidence that radiographic evidence of hydronephrosis or stone surgery were associated with more abnormal kidney function after the first stone event. Nonetheless, the acute and transient decline in GFR due to an obstructive nephropathy at the time of the stone event may result in nephron loss that is eventually compensated for by hyperfiltration of the remaining nephrons. It is worth noting that acute kidney injury is an important risk factor for CKD [26] and the transient rise in serum creatinine at the time of a stone event may likewise contribute to CKD. Also, transient albuminuria may reflect glomerular injury from tubular obstruction with renal vasoconstriction, inflammation and ischemia.[27] Further studies are needed to clarify if the number of stone events is predictive of long-term CKD among stone formers, particularly stone events with acute kidney injury.

There were several notable strengths and potential limitations to this study. The combination of comprehensive chart review, administered surveys, and laboratory testing allowed for detailed characterization of risk factors and kidney function among carefully validated

incident symptomatic stone formers and controls. However, since stone formers were only identified after their first stone event, information on their kidney function prior to the stone event was limited. In particular, we could not rule out the possibility that the elevated cystatin C and proteinuria precedes the first stone event. From what was available in the medical record, stone formers were not more likely to have a diagnosis of CKD, have had serum creatinine testing, or have higher serum creatinine levels than controls before their stone event. Kidney function was tested across two consecutive study visits 90 days apart to assess for chronicity. Nonetheless, participation was lower at visit 2, especially for stone formers (only 76% completed visit 2). The burden of another 24-h urine collection was often cited as a reason for non-participation at visit 2. Over- and under-collection of urine was an expected problem with the 24-h urine collections, but adjustment for 24-h urine creatinine in the multivariable analysis helped correct for this. Finally, a direct measurement of GFR (e.g. iothalamate clearance) was lacking and would be needed to clarify if the higher cystatin C in stone former was due to the GFR or non-GFR determinants of cystatin C.[14]

CONCLUSION

This prospective study increases understanding of the previously reported risk of CKD in stone formers. Incident stone formers demonstrated a transient rise in serum creatinine and urine albumin that subsequently resolved. However, they had persistently higher serum cystatin C levels and non-albumin proteinuria. Clarification of the non-albumin proteins that contribute to proteinuria in stone formers is needed and may provide insights into the pathophysiology of CKD in stone formers. Identification of whether the higher cystatin C in stone formers is due to GFR reduction or other non-GFR biology is needed. Given its prognostic importance,[28] the role of routine cystatin C testing in stone formers deserves consideration. Further study is needed to determine if these early kidney function findings in stone formers contribute to the long-term risk of CKD and end-stage renal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The investigators thank Ruth Kraft for her work as study coordinator and Cynthia Nosek for her work as nurse abstractor on this project.

Funding Sources:

This project was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (Mayo Clinic O'Brien Urology Research Center, DK100227 and DK83007) and made possible by the Rochester Epidemiology Project (AG034676), Mayo Clinic's Center for Clinical and Translational Science (UL1 TR000135), and the Mayo Clinic's Nephrology- Urology Summer Undergraduate Research Fellowship program (DK100227) from the National Institutes of Health, U.S. Public Health Service. The funding sources had no role in the study design, conduct, or reporting.

Glossary

CKD	chronic kidney disease

GFR	glomerular filtration rate
$eGFR_{Cr}$	serum creatinine based estimated glomerular filtration rate
UTI	urinary tract infection

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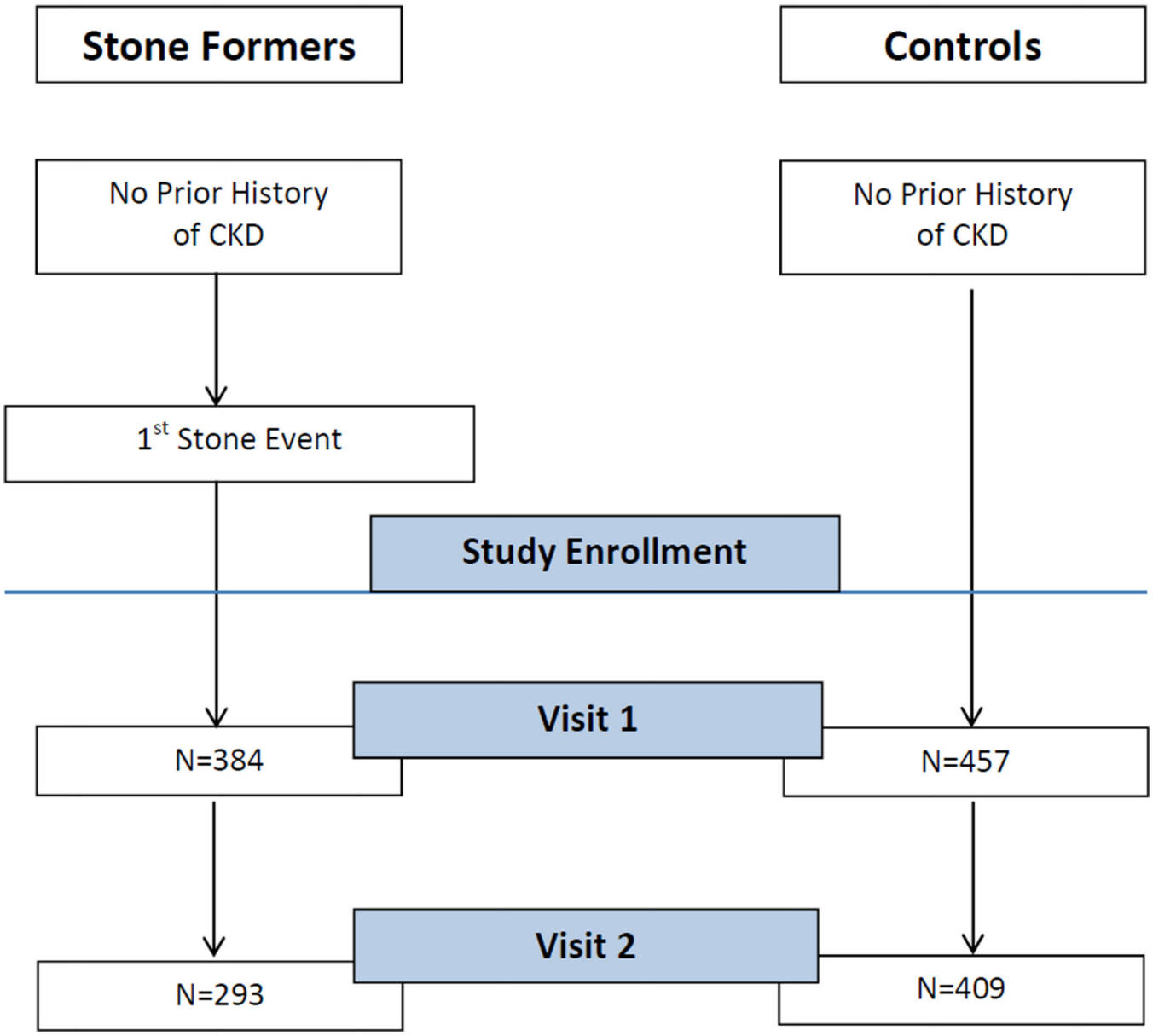

Figure 1.
Flowchart diagram of matched cohort study design

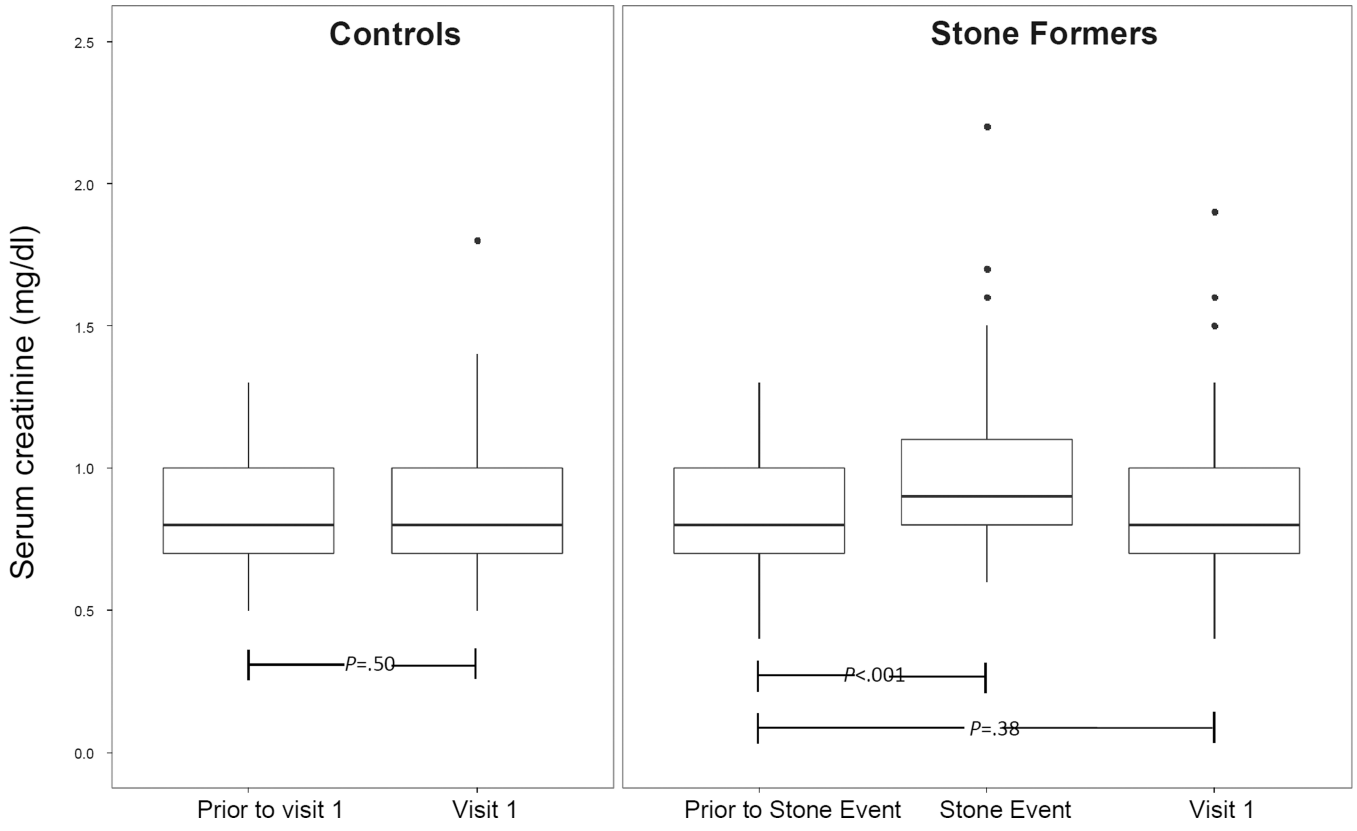

Figure 2.
Box plots of the serum creatinine level trends until the time of study participation (Visit 1).

Table 1

Baseline patient characteristics and comorbidities in stone formers and controls

Clinical Characteristics	Stone Former (N=384)	Controls (N=457)		Age and sex adjusted estimates[a]
	Mean (SD)	*Difference*		*P*
Age at 1st visit, years	46.6 (14.4)	45.6 (14.7)	0.76	.45
Body mass index, k/mg^2	30.6 (7.1)	28.1 (5.7)	2.42	<.001
	n (%y)	*OR*		*P*
Male	204 (53.1%)	221 (48.4%)	1.19	.22
White race[b]	365 (95.1%)	431 (94.3%)	1.12	.73
Hypertension[c]	126 (32.8%)	93 (20.4%)	1.98	<.001
Diabetes[c]	45 (11.7%)	37 (8.1%)	1.47	.11
Gout[c]	17 (4.4%)	10 (2.2%)	1.97	.10
History of urinary tract infection[c]	152 (39.6%)	149 (32.6%)	1.81	<.001
Diarrhea or loose stools[c]	78 (20.3%)	22 (4.8%)	5.16	<.001
Gastric bypass surgery[c]	19 (4.9%)	13 (2.8%)	1.86	.10
Works in hot temperatures	129 (33.6%)	117 (25.6%)	1.42	.03
Heat cramps	54 (14.1%)	32 (7.0%)	2.12	.002
Calcium supplement[c]	119 (31.0%)	111 (24.3%)	1.53	.01
Family history of kidney stones[c]	174 (45.3%)	85 (18.6%)	3.69	<.001

[a]Multivariable linear regression models were used for continuous variables and multivariable logistic regression models were used for categorical variables

[b]For race variable, if “other” or “unknown,” then considered “non-white.”

[c]Information regarding these patient characteristics was obtained from both the survey and the medical record.

Table 2

Baseline serum and urine chemistries in stone formers and controls

Serum and urine chemistries	Stone Former (N=384)	Controls (N=457)	Age and sex adjusted estimates[a]	
	Mean (SD)		*Difference*	*P*
Bicarbonate, mmol/L	26.4 (2.3)	26.7 (2.2)	−0.32	.05
Serum Calcium, mg/dL	9.4 (0.5)	9.3 (0.6)	0.10	.01
Serum Phosphate, mg/dL	3.5 (0.7)	3.4 (0.5)	0.08	.05
Serum Uric Acid, mg/dL	5.6 (1.4)	5.1 (1.5)	0.44	<.001
Urine Calcium, mg/24hr	206 (125)	154 (92)	48.8	<.001
Urine Chloride, mmol/24hr	126 (67)	118 (63)	5.98	.18
Urine Citrate, mg/24hr	615 (367)	578 (292)	31.7	.18
Urine Magnesium, mg/24hr	99 (47)	91 (47)	5.91	.07
Urine Oxalate, mmol/24hr	0.23 (0.13)	0.27 (0.12)	−0.04	.001
Urine Phosphate, mg/24hr	746 (345)	647 (311)	83.1	<.001
Urine Potassium, mmol/24hr	50 (24)	52 (26)	−3.67	.03
Urine Sodium, mmol/24hr	138 (70)	128 (66)	8.28	.08
Urine Uric Acid, mg/24hr	444.49 (205)	433 (194)	4.76	.73
Urine Volume, mL	1743.37 (746)	1828 (844)	−105.4	.06
Urine Creatinine, mg/24hr	1166 (503)	1056 (461)	84.8	.004
Urine pH	6.10 (0.52)	6.19 (0.60)	−0.07	.07

[a] Multivariable linear regression models were used

Table 3

Kidney function in stone formers vs controls at visit 1 and 2

Kidney function	Stone Formers	Controls	Age and sex adjusted estimates†		Multivariable adjusted estimates[a]	
First Visit	***N=384***	***N=457***				
	Mean (SD)		***Difference***	***P***	***Difference***	***P***
Serum Creatinine mg/dL	0.86 (0.20)	0.84 (0.19)	0.01	.23	0.001	.96
Cystatin C mg/L	0.83 (0.21)	0.72 (0.16)	0.11	**<.001**	0.09	**<.001**
Urine Total Protein mg/24hr	34.2 (38.6)	19.7 (20.0)	14.1	**<.001**	9.2	**<.001**
	n (%)		***OR***	***P***	***OR***	***P***
Urine Albumin >5mg (vs. ≦ 5mg)	127 (34.1%)	108 (24.1%)	1.62	**.002**	1.65	**.02**
Urine Albumin >30mg (vs. ≦ 30 mg)[b]	20 (5.4%)	10 (2.2%)	2.48	**.02**	-	-
$eGFR_{Cr}$<60 ml/min/1.73 m^2[b]	18 (4.7%)	12 (2.6%)	1.80	.13	-	-
Urine Albumin >30mg or $eGFR_{Cr}$<60 ml/min/1.73 m^2 [b]	36 (9.4%)	22 (4.8%)	2.01	**.01**	-	-
Second Visit	***N=293***	***N=409***				
	Mean (SD)		***Difference***	***P***	***Difference***	***P***
Serum Creatinine mg/dL	0.86 (0.20)	0.83 (0.16)	0.005	.73	0.003	.88
Cystatin C mg/L	0.82 (0.23)	0.72 (0.16)	0.10	**<.001**	0.08	**<.001**
Urine Total Protein mg/24hr	33.2 (49.6)	19.6 (32.9)	13.2	**<.001**	8.5	.07
	n (%)		***OR***	***P***	***OR***	***P***
Urine Albumin >5mg (vs. ≦ 5mg)	63 (31.7%)	69 (21.0%)	1.76	**.006**	0.98	.95
Urine Albumin >30mg (vs. ≦ 30 mg) [b]	11 (5.5%)	10 (3.0%)	1.90	.16	-	-
$eGFR_{Cr}$<60 ml/min/1.73 m^2 [b]	4 (2.5%)	4 (1.2%)	1.94	.37	-	-
Urine Albumin >30mg or $eGFR_{Cr}$<60 ml/min/1.73 m^2 [b]	15 (5.7%)	14 (3.5%)	1.64	.19	-	-

[a] Multivariable linear regression models were used for continuous variables; multivariable logistic regression models were used for categorical variables. Covariates include all patient characteristics from table 2: age, sex, body mass index, race, history of hypertension, diabetes, gout, history of urinary tract infection, diarrhea, gastric bypass surgery, working in hot temperatures, heat cramps, calcium supplement use, family history of stones, and all serum (bicarbonate, calcium, phosphate, uric acid) and urine (calcium, chloride, citrate, magnesium, oxalate, phosphate, potassium, sodium, uric acid, volume, creatinine and pH) chemistries.

[b] Multivariable models were not fit for these outcomes due to low power.