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Risk factors for chronic kidney disease in persons with kidney stones: Case-control study in Olmsted County, Minnesota

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Abstract

Background—Kidney stones are associated with an increased risk for chronic kidney disease but risk factors in the general community are poorly defined.

Study Design—A nested case-control study was performed among Olmsted County, Minnesota residents who presented with a kidney stone at the Mayo Clinic between 1980 and 1994 to contrast kidney stone patients who developed chronic kidney disease to a group who did not.

Setting and Participants—Subjects were selected from the Rochester Epidemiology Project, an electronic linkage system between health care providers in Olmsted County, Minnesota. Cases were identified by diagnostic code for chronic kidney disease and confirmed to have an estimated glomerular filtration rate <60 ml/min/1.73 m². Controls were matched 2:1 to cases on age, sex, date of first kidney stone, and length of medical record.

Predictor—Charts were abstracted to characterize stone disease, hypertension, diabetes, obesity, tobacco use, ileal conduit, symptomatic stones, type and number of stones, urinary tract infections, number and type of surgical procedures, and medical therapy.

Outcomes and Measurements—Kidney stone patients with CKD were compared to matched stone patients without CKD.

Results—There were 53 cases and 106 controls with a mean age of 57 years at first stone event and 59% were men. Among kidney stone patients, cases with CKD were significantly more likely ($P<0.05$) than controls to have had a history of diabetes (41.5% vs 17.0%), hypertension (71.7% vs 49.1%), frequent urinary tract infections (22.6% vs 6.6%), struvite stones (7.5% vs 0%), and allopurinol use (32.1% vs 4.7%) based on univariate analysis.

Limitations—Potential limitations include limited statistical power to detect associations, incomplete data from 24 hour urine studies, and that stone composition was not always available.

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Disclosure

All the authors declared no competing interests.

Conclusion—As in the general population, hypertension and diabetes are associated with an increased risk of chronic kidney disease amongst patients with kidney stones. However, other unique predictors were identified in kidney stone patients that increased the possibility of chronic kidney disease. Further studies are warranted to elucidate the nature of these associations.

Index words

Nephrolithiasis; chronic kidney disease; kidney stone

Introduction

Kidney stones are a common condition associated with significant morbidity, since up to 12% of men and 5% of women will have one symptomatic kidney stone by the age of 70 and recurrence rates are estimated at 50%. (1) In addition, the economic impact of kidney stone disease is significant with a total estimated economic burden in the United States recently estimated at \$5.3 billion. (2) Although the majority will have no long-term consequences of a stone event, kidney stone disease has previously been suggested as a potential risk factor for chronic kidney disease (CKD). (3,4) Among those kidney stone patients with CKD, those who might progress to end-stage renal disease (ESRD) are of particular interest given the associated high morbidity, mortality and healthcare costs.

CKD is equally common, estimated to affect 11% of men and 15% of women in the United States. (5) Although studies have suggested that kidney stone disease is associated with CKD, the mechanisms of this association have not been fully elucidated. USRDS data from 2001–2005 indicate that of all patients starting dialysis in that time period, 0.2% had kidney stones identified as the cause of ESRD at a median age of 65. (6) Analysis in 1996 has revealed that 20% of patients with staghorn calculi show evidence of progressive renal disease after treatment, even though open lithotomy already was uncommon at that time. (7) Failure to render a staghorn patient stone free after surgery increased CKD risk, and this outcome was more frequent when the stone contained struvite. Fortunately struvite stones are relatively uncommon in the United States, making up less than 15–20% of kidney stones. (8) Severe and recurrent stone disease, particularly from rarer genetic disorders (e.g., primary hyperoxaluria, cystinuria) has also been associated with ESRD. (9)

Previous studies that have examined risk factors for CKD among kidney stone patients were performed in tertiary settings amongst patients referred to a specialist focused on prevention of recurrent stones (9–11). This group of patients likely has a more severe form of kidney stone disease and/or other differentiating features, raising the question of referral bias and applicability of the results to the general population. Many kidney stone patients in the general population may never see specialist for stone prevention and the composition of their kidney stones may be unknown. Therefore, the potential link between their kidney stone disease and CKD may go unrecognized. The nature and potential risk factors for CKD among such kidney stone patients in the community is less clear. Therefore, we investigated risk factors for CKD amongst stone-formers in the Olmsted County community. We hypothesized that there are clinical characteristics that differentiate kidney stone patients who develop CKD from those who do not.

Methods

Participants

More than 95% of the population in Olmsted County has at least one clinic visit with a health care provider every 2 to 3 years, allowing complete enumeration of the local population. Diagnostic codes (manually or automatically coded from the final diagnoses in clinical notes)

dating back to 1935 are indexed and linked among virtually all Olmsted County patients in the Rochester Epidemiology Project (REP). This unique database allows an electronic linkage system to provide comprehensive data collection on nearly all residents in Olmsted County, Minnesota. (12)

Following approval by the Mayo Clinic Institutional Review Board, the REP was used to identify the cohort of all Olmsted County residents who had a kidney stone diagnosis at the Mayo Clinic between 1980 and 1994 using International Classification of Diseases (ICD)-9 codes 592, 594, and 274.11 and equivalent Hospital Adaptation of the International Classification of Diseases (HICDA)-8 codes. After excluding patients who had denied access to their medical records, 2077 patients were identified (64% male; 44.5 ± 17.4 years old at diagnosis). Within this cohort of 2077 kidney stone patients, a nested case-control study was performed for the outcome of CKD (Figure 1).

Case Definition—For this study CKD cases were identified on the basis of an ICD-9 code 585 (chronic renal failure) assigned after their first stone event. The charts of all cases were then manually reviewed to verify the presence of at least two separate serum creatinine measurements 3 months apart that yielded an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m² using the 4-variable Modification of Diet in Renal Disease (MDRD) study equation. (13) Only serum creatinine levels at least 3 months from any hospitalization were used for this purpose, in order to avoid misclassification of cases with acute renal failure. Serum creatinine measures prior to institutional use of standardized creatinine method at Mayo Clinic in October 2006 were corrected to standardized levels. (14) ESRD was defined as a sustained estimated GFR <15 mL/min/1.73 m² by the MDRD study equation, or the need for renal replacement therapy (long term dialysis or kidney transplantation).

Control Definition—For each case, 2 kidney stone controls without CKD (no diagnosis code of 585 up until the case's CKD date) were matched based on sex, age at first stone, year at first stone, and length of medical record using a computer algorithm applied to the values of each matching factor.(15) After manual chart review, cases and controls were retained if they were Olmsted County residents at the index kidney stone date and their kidney stone disease was verified by either radiographic imaging (kidney ureter bladder film (KUB), abdominal X-ray (XR), intravenous pyelogram (IVP), or computed tomography (CT)); or a symptomatic kidney stone episode was documented in the record. Controls with an estimated GFR <60 mL/min/1.73 m² before their matched case was diagnosed with CKD were replaced with new controls. Data for matched controls was abstracted from the medical record until the case developed CKD.

Predictors evaluated

Charts were manually abstracted for height, weight, number of kidney stone episodes, type of kidney stone, tobacco use, ileal conduit, symptomatic stone events (hematuria, flank or groin pain during an emergency room or clinic visit), number of urinary tract infections, number and type of surgeries for stone disease including ureteroscopic procedures (open lithotomy, ESWL, percutaneous, ureteroscopic, and laparoscopic surgery), and type of medical treatment (allopurinol, citrate, thiazide, orthophosphate, and other). Diabetes mellitus and hypertension were deemed present if clinically diagnosed by their provider per documentation in the record, or based upon manual chart review with a diagnosis of diabetes for 2 random fasting blood glucose >126 mg/dl and hypertension if BP $>140/90$ mmHg. Relevant laboratory parameters were also collected including baseline and follow-up serum creatinine, 24-hour urine chemistries, and urinalysis at the time of kidney stone onset.

Statistical Analysis

The association between CKD and each of the predictors was evaluated by fitting conditional logistic regression models. In order to obtain finite odds ratio (OR) estimates, an exact conditional logistic regression model was fit for each univariate model that included a predictor that was prevalent among the cases, but not prevalent among the controls (i.e. quasi-complete separation of data). Associations were summarized using ORs with corresponding 95% confidence intervals (CI). A multivariable exact conditional logistic regression model was fit using all of the predictors with a p-value < 0.10 based on the univariate analyses. All reported p-values were two-sided, and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS v9.1 software (SAS Institute, Cary, NC). The case-control design (53 cases and 106 controls) allowed for sufficient power (80%) to detect OR's from 2.6 – 3.1 for common (15–40%) exposures, with alpha of 0.05 and two-sided tests.

Results

There were 61 potential cases with a diagnosis of chronic renal failure among Olmsted County, MN kidney stone patients evaluated at the Mayo Clinic between 1980 and 1994 that were confirmed with an estimated GFR <60 ml/min/1.73 m². After excluding 8 of these cases in whom CKD preceded their first kidney stone episode, there were 53 eligible cases that were then age and sex matched to 106 kidney stone controls without CKD. Baseline gender (41% female) and age at index date were similar in each group (Table 1). Mean age at the time of CKD diagnosis was 66.1 (±17.3) years for cases. Duration of time from first kidney stone diagnosis to matched case's CKD date and final estimated GFR at the case's CKD date are summarized in Table 1. Among the cases, 36% (19 of 53) had end-stage renal disease at last follow-up.

Table 2 lists clinical characteristics compared between the two groups of kidney stone patients with and without CKD. Significant differences were found between the case and control groups regarding known CKD risk factors such as hypertension (OR 3.57, p=0.004) and diabetes (OR 4.27, p=0.001). Obesity (OR 1.92) and tobacco use (OR 1.77) were also more common amongst kidney stone CKD patients, but did not achieve statistical significance. Recurrent (6 or more) urinary tract infections (UTIs) were more frequently present amongst kidney stone patients with CKD (OR 5.81, p=0.004). Previous construction of an ileal conduit was also associated with an increased CKD risk (OR 7.69, p=0.07); however, the absolute number of affected cases was small (3 CKD kidney stone patients and no control kidney stone patients).

Comparisons were made between the case and control groups regarding stone burden, treatment, events, and type of stone. There was no significant difference in the number of stone episodes between the individual groups. However, CKD patients were more likely to have a documented struvite stone (4 cases vs 0 controls; OR 15.61, p=0.01). Although it is well known that struvite stones are caused by urinary tract infection with a urease positive organism, just 2 of the 4 cases with struvite stones were among the 12 cases with 6 or more UTIs. However, about half of the patients in both groups did not have their kidney stone identified, raising the possibility that additional struvite stone cases were in the CKD group. The same possibility exists for uric acid stones.

Patients who had documented clinical symptoms of kidney stones such as flank or groin pain, hematuria, or dysuria did not demonstrate an increased risk for CKD. The number or type of surgical procedures including open lithotomy also did not increase risk of CKD. Unfortunately, urine chemistry data was not obtained in enough kidney stone patients within this historical cohort in order to analyze urinary composition in relationship to CKD risk. Patients that formed a documented uric acid stone were more likely to develop CKD (OR 3.10), although this association was not significant (p=0.10). There was an almost 10.4-fold increased risk for CKD

among kidney stone patients taking allopurinol. Use of thiazides or citrate for any reason did not differ significantly between the groups.

Finally, a multivariable model was constructed using all of the CKD predictors with a p-value < 0.10 in the univariate analyses. Diabetes, frequent UTI's (>6), and allopurinol therapy each attained statistical significance at the 0.05 level as predictors of CKD risk in this kidney stone cohort, while hypertension, obesity, ileal conduit, and type of stone did not. (Table 3).

Discussion

Previous studies have shown an association between kidney stone disease and CKD in the general population but did not identify features that may increase this risk. (4) In this population-based sample of kidney stone patients, we have identified features that characterize kidney stone patients who develop CKD from those who do not. As might be expected, the well-established risk factors hypertension and diabetes were significantly associated with CKD risk in the stone forming cohort. The presence of struvite, recurrent UTIs, and prior allopurinol use were also more common in kidney stone patients with CKD. Formation of uric acid stones and ileal conduits had borderline statistical significance as a risk factor for CKD. Stone number and stone procedures did not have evident associations with CKD risk.

It is not surprising that hypertensive and diabetic patients with kidney stone disease have an increased risk for CKD since diabetes and hypertension are well-known to be associated with CKD in the general population. (16) The links between kidney stone disease and both hypertension and diabetes are also complex, since both have been described as risk factors for stone formation in previous studies. (17,18) Diabetes appears to particularly increase risk for uric acid stones. (19) Since both hypertension and diabetes were heavily enriched among kidney stone patients that developed CKD, it is likely that they explain a significant portion of the CKD risk in this kidney stone cohort.

Obesity is another increasingly common condition associated with multiple medical morbidities, including CKD and kidney stone disease. In our study obesity, defined as a body mass index (BMI) greater than 30 kg/m², was more common amongst kidney stone patients with CKD although this association did not achieve statistical significance (OR=1.92, p=0.07). In a previous analysis of NHANES data, obesity was also suggested to act synergistically with kidney stone disease to increase risk of reduced GFR. (20)

Olmsted County patients with kidney stones and CKD were also approximately a decade older than the previously described cohorts of patients with incident stones (21,22). It is not clear whether age was a factor that increased the risk for comorbidities associated with CKD or made these kidney stone patients with multiple comorbidities more susceptible to CKD. However, multiple traits common to kidney stone disease and CKD (hypertension, diabetes, obesity) may independently increase the risk of both in parallel. This study did not assess whether kidney stone patients with one of these other risk factors differ in their risk of CKD then compared to patients without kidney stone disease.

The use of allopurinol was significantly associated with CKD in the kidney stone cases (OR 10.38, p<0.001). This may have been due to common use of this drug for treatment of hyperuricemia secondary to CKD. We were not able to determine if allopurinol was used for hyperuricemia or for primary treatment of stone disease. Development of uric acid stones was also more common amongst CKD patients (OR 3.10), although this association was not statistically significant (p=0.10). Estimates of CKD risk with stone type are limited among kidney stone patients sampled from the community because stone analysis has often not been performed.

Growth of struvite stones is due to the concurrent generation of ammonia and alkaline urine by urea splitting organisms. At such urine pHs, ammonium ions are toxic to renal tubular cells and can lead to long-term injury. (3) CKD secondary to chronic pyelonephritis can also develop in the setting of repeated UTIs not caused by urease producing organisms (23). Furthermore, large staghorn calculi that are characteristic of struvite stones could potentially cause renal obstruction and damage. Our study confirmed a significantly greater risk of CKD in patients with a diagnosis of struvite stone disease as well as those with 6 or more distinct urinary tract infections.

Similar factors may underlie the increased risk for CKD in patients with recurrent UTI's and ileal conduits, since ileal conduits may predispose to recurrent infections. Ileal conduits are independently associated with kidney stones as well. Madersbacher and colleagues reported that kidney stones were a long term complication in ileal conduit surgery in 9% of patients studied. In this report, alteration of kidney function and morphology was found in 27% of patients with ileal conduits and 23% of patients developed symptomatic UTIs. (24) Our study confirms an association of ileal conduits with decreased renal function in patients with kidney stone disease. Further studies are needed to elucidate the factors that underlie this association, for example if toxins produced by microbial pathogens could contribute to renal fibrosis.

It is not clear why the number of recurrent stone events did not appear to correlate with increased risk for progression to CKD as was observed in previous studies. (10) Amongst 171 patients with idiopathic calcium stones Marangella and colleagues studied, the 30 with reduced GFR (estimated GFR < 80 mL/min/1.73m²) had severely recurrent disease with approximately one stone per patient per year. However, the number of patients in our study with multiple stone events (3 or more) was fairly small [12 cases (22.6%) and 16 controls (15.1%)]. We also did not find that the type of surgical procedure or the number of surgical procedures performed for stone disease was a predictor of CKD. For example, it has been proposed that shock wave lithotripsy can produce renal damage (25), hypertension (26,27), and diabetes mellitus. (28) However, we did not find increased risk of CKD amongst those treated with extracorporeal shock wave lithotripsy (ESWL). Perhaps not surprisingly, a history of open lithotomy did appear to increase the long term risk of CKD in our cohort (OR 2.18), although this association did not achieve significance in our study and the number of these procedures was small. Fortunately, open lithotomy is rarely needed for stone disease today.

The current study has several limitations. It is retrospective and subject to the biases inherent to such a study design. A relatively small number of cases were present (N=53), although this was compensated by matching 2 controls per case. As is common in a general population, many stones were not analyzed and few patients had 24 hour urine chemistry testing. Therefore, without knowledge of stone composition and/or urine composition it is difficult to make associations between particular types of stones and CKD. Nevertheless, calcium-based stones are by far the most common in the stone-forming population and these are well-represented in our study. Additionally, our study supports that struvite stones are indeed associated with development of CKD and these patients require special attention. Finally, there was also no uniform documentation regarding diet and medical therapy for kidney stone disease which limits conclusions regarding these treatment factors and CKD.

Among this population-based, case-control cohort of patients with kidney stones we demonstrated a higher risk for progression to CKD in kidney stone patients who not only have traditional risk factors (such as diabetes and hypertension), but also for those with recurrent UTI's, struvite stones, history of allopurinol use, and possibly uric acid stones, ileal conduits, and obesity. Although there was no evidence that shock wave lithotripsy was more common among kidney stone patients with CKD, open lithotomy was more prevalent. Clinically, these findings support a rationale for closer monitoring of renal function in all stone patients,

particularly those with the above risk factors. It also suggests a rationale for prompt treatment of infections and aggressive treatment of diabetes, hypertension, obesity, and smoking cessation in kidney stone patients. It is not known if patients with diabetes or hypertension and kidney stones are more likely to develop CKD than patients with diabetes or hypertension but without kidney stones. These findings also suggest that further research is needed to elucidate the nature of these associations (to determine causality vs. association), to determine pathogenetic mechanisms of kidney injury in kidney stone disease, and to determine risk factors amenable to intervention.

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Figure 1. Study Design

CKD = chronic kidney disease, MDRD = 4-variable Modification of Diet in Renal Disease study equation

Table 1

Baseline and follow-up characteristics of kidney stone cases with CKD and matched controls with kidney stones but without CKD

	Cases (N=53)	Controls (N=106)
Gender		
Male	31 (58.5%)	62 (58.5%)
Female	22 (41.5%)	44 (41.5%)
Age at first stone episode (years)		
Mean (SD)	56.5 (19.0)	57.9 (16.3)
Median	58.1	58.3
First and third quartiles.	44.1–71.7	45.7–68.6
Age at time of CKD diagnosis (years)		
Mean (SD)	66.1 (17.3)	--
Median	68.9	
First and third quartiles.	56.1 – 81.1	--
Duration of follow-up (years) [†]		
Mean (SD)	9.7 (12.0)	10.4 (10.3)
Median	6.5	7.7
First and third quartiles.	0.02 – 14.8	2.5 – 14.3
Final estimated GFR (mL/min/1.73m ²) [‡]		
Mean (SD)	32.0 (15.5)	78.4 (16.6)
First and third quartiles.	16.0 – 43.9	67.9 – 86.8

CKD = chronic kidney disease. GFR = Glomerular filtration rate.

[†] Duration of time from the patient's first kidney stone diagnosis to the matched case's CKD diagnosis date.

[‡] Based on closest creatinine within 2 years of matched case's CKD diagnosis date.

Table 2

Prevalence of risk factors in kidney stone patients with CKD and matched kidney stone patients without CKD.

Predictor	Cases N=53 (%)	Controls N=106 (%)	OR (95% CI)	P-value
Symptomatic kidney stone	62.3	67.0	0.81 (0.38–1.74)	0.7
Hypertension	71.7	49.1	3.57 (1.49–8.55)	0.004
Diabetes	41.5	17.0	4.27 (1.77–10.29)	0.001
BMI > 30 kg/m ²	50.9	36.8	1.92 (0.94–3.92)	0.07
Ileal Conduit	5.7	0.0	7.69 (0.83-infinity) [†]	0.07
Tobacco Use	62.3	50.0	1.77 (0.86–3.64)	0.1
<u>Number of UTI</u>				0.04 global
0	45.3	62.3	Referent	Referent
1	20.8	17.9	1.65 (0.67–4.07)	0.3
2 to 5	11.3	13.2	1.11 (0.40–3.06)	0.8
6+	22.6	6.6	5.81 (1.75–19.33)	0.004
<u>Number of stone episodes</u>				0.6 global
1	56.6	63.2	Referent	Referent
2	20.8	20.8	1.15 (0.48–2.77)	0.8
3+	22.6	16.0	1.54 (0.67–3.54)	0.3
<u>Stone type</u>				0.006 global
Calcium-based	24.5	38.7	Referent	Referent
Unknown	45.3	50.9	1.49 (0.62–3.73)	0.4
Uric Acid	15.1	7.5	3.10 (0.79–13.14)	0.1
Struvite	7.5	0.0	15.61 (1.83-infinity) [†]	0.01
Other	7.5	2.8	5.72 (0.72–70.59)	0.1
<u>Medical Therapy</u>				
Allopurinol	32.1	4.7	10.38 (3.02–35.62)	<0.001
Citrate	5.7	2.8	2.00 (0.40–9.91)	0.4
Thiazide	37.7	32.1	1.30 (0.64–2.65)	0.5
<u>Total number of surgical procedures</u>				0.9 global
0	52.8	50.0	Referent	Referent
1	22.6	26.4	0.82 (0.38–1.79)	0.6
2	13.2	13.2	0.94 (0.34–2.61)	0.9
3+	11.3	10.4	1.06 (0.36–3.11)	0.9
<u>Type of surgical procedure</u>				
Cystoscopy/ureteroscopy	18.9	29.2	0.58 (0.27–1.27)	0.2
Open lithotomy	15.1	7.5	2.26 (0.77–6.66)	0.1
ESWL	9.4	13.2	0.70 (0.25–2.00)	0.5
PCNL	3.8	3.8	1.00 (0.08–9.42) [†]	0.9
Ureteroscopy	17.0	12.3	1.47 (0.58–3.70)	0.4

<u>Predictor</u>	<u>Cases N=53, (%)</u>	<u>Controls N=106 (%)</u>	<u>OR (95% CI)</u>	<u>P-value</u>
Laparoscopic Nephrolithotomy	0.0	0.9	2.00 (0–78.00) [†]	0.9

OR = odds ratio. UTI = urinary tract infection. BMI = body mass index. ESWL = Extracorporeal shock wave lithotripsy. CKD = chronic kidney disease. PCNL = Percutaneous nephrolithotomy

[†]Results are from fitting an exact conditional logistic regression model..

Table 3

Predictors of CKD in a multivariable model.

<u>Predictor</u>	<u>OR (95% CI)</u>	<u>P-value</u>
Hypertension	1.53 (0.46–5.57)	0.6
Diabetes	3.49 (1.13–12.92)	0.03
BMI > 30 kg/m ²	0.93 (0.31–2.69)	0.9
Ileal conduit	1.49 (0.91–infinity)	0.8
UTI 6+ (vs. < 6)	4.83 (1.00–34.90)	0.05
Struvite stone type (vs. all others)	4.52 (0.45–infinity)	0.2
Allopurinol	7.86 (1.79–52.95)	0.003

OR = odds ratio. UTI = urinary tract infection. CKD = chronic kidney disease. BMI = body mass index.