

REVIEW ARTICLE



Rising occurrence of hypocitraturia and hyperoxaluria associated with increasing prevalence of stone disease in calcium kidney stone formers

Ramy F. Youssef^{ca*}, Jeremy W. Martin^{ab*}, Khashayar Sakhaee^b, John Poindexter^b, Sharmin Dianatnejad^a, Charles D. Scales^c, Glenn M. Preminger^c and Michael E. Lipkin^c

^aDepartment of Urology, University of California, Irvine, CA, USA; ^bDepartment of Internal Medicine, Charles and Jane Pak Center of Mineral Metabolism and Clinical Research, University of Texas Southwestern, Dallas, TX, USA; ^cDivision of Urology, Duke University Medical Center, Durham, NC, USA

ABSTRACT

Objective: To evaluate metabolic risk factors in calcium kidney stone formers from two different decades, comparing changes in metabolic profiles over time.

Methods: A retrospective analysis was performed of calcium kidney stone formers who underwent metabolic evaluation of urolithiasis with 24-hour urine collections at a single institution. There were 309 patients evaluated from 1988 to 1994 (Group A), and 229 patients from 2007 to 2010 (Group B). A comparison between both groups was performed to assess changes in demographics and in metabolic stone profiles.

Results: Comparing Group A to Group B, the percentage of females increased from 43 to 56%, obese patients (BMI \geq 30) increased from 22 to 35%, and patients \geq 50 years increased from 29 to 47% (all $p < 0.005$). A greater percentage of patients had hypocitraturia in the recent cohort (46–60%, $p = 0.001$), with hypocitraturia significantly more frequent in obese patients ($p = 0.005$). Hyperoxaluria was also increased in Group B compared to Group A (23–30% $p = 0.07$), a finding that was significant in males (32–53%, $p = 0.001$).

Conclusions: Urolithiasis has increased in females, obese, and older patients, consistent with population-based studies. We report a rising incidence of hypocitraturia and hyperoxaluria in the contemporary cohort, particularly in obese patients and in males, respectively. Further studies are needed to better characterize the metabolic changes corresponding to the increase in stone disease.

Abbreviations: BMI: Body mass index; MS: Metabolic syndrome; UA: uric acid; KCit: Potassium citrate; NHANES: National Health and Nutrition Examination Survey

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Introduction

Urolithiasis has increased in recent decades in the US, a trend observed across all ages, genders and ethnic groups [1,2]. The continuing rise in stone disease represents a major health and economic burden on the population [3]. While earlier reports from the National Health and Nutrition examination Survey (NHANES) from 1976 to 1980 and 1988 to 1994 reported the prevalence of stone disease at 3.8 and 5.2%, respectively, more recent data from 2007 to 2010 indicated an 8.8% prevalence of kidney stones, with 10.6% in men and 7.1% in women [1,4]. Although urolithiasis has historically been described as more frequent in men, the percentage of females with stone disease is likely rising, with a nationwide sample reporting a decrease in male:female ratio from 1.7:1 to 1.3:1 [5].

This increase in stone disease prevalence has been attributed to dietary, environmental and lifestyle changes. Concomitant increases in obesity, diabetes and metabolic syndrome over the recent decades have been linked with

the development of stone disease in many reports [6,7]. Obesity and diabetes are associated with insulin resistance and metabolic derangements including hypocitraturia, hypercalciuria, hyperoxaluria and increased urine acidity, each of which can contribute to development of stone disease [8–10]. Other factors, including the western diet, with its high oxalate, protein and sodium content and environmental factors such as global warming have also been implicated in the rise in stone disease [11].

Temporal changes in urinary metabolic abnormalities of stone formers are interesting to evaluate, as they may inform the predominant pathophysiologic mechanisms behind the increased prevalence. In this study, our objective was to evaluate the urinary biochemical risk factors of calcium kidney stone formers at a single institution across two time periods, 1988–1994 and 2007–2010, corresponding to the large NHANES collection periods, and determine if epidemiological characteristics and metabolic diagnoses in kidney stone formers have differed over time.

Methods

Patient selection

Institutional review board approval was obtained for this study. We performed a retrospective analysis of patients who underwent metabolic evaluation for urolithiasis with 24-hour urine collections at a single institution. All patients with Ca kidney stones were included. Exclusion criteria included age 21 or younger, chronic kidney disease stages 4 or 5 and patients with non-calcium stones.

Two temporally distinct groups of patients were compared to assess changes in demographics and metabolic profiles over time. The first group (Group A) included 309 stone patients evaluated from 1988 to 1994, while the second group (Group B) included 229 patients from 2007 to 2010. These time periods were chosen to represent the corresponding NHANES collection periods.

Data collection and measurements

Demographic characteristics of stone formers, including age, gender and BMI, were collected at the ambulatory patient visit. A BMI of ≥ 30 was considered obese while a BMI of ≥ 25 but < 30 was considered overweight. For 2 weeks prior to 24-hour urine collection, patients were instructed to hold all directed medical therapy that might affect urinary stone metabolic profiles. Patients then underwent 24-hour urine collections to evaluate for urinary metabolic abnormalities.

Data from 24-hour urine collections were interpreted according to reference values as used in our clinical practice. Low urinary volume was defined as < 2.5 L. Hypercalciuria was defined to be urinary calcium ≥ 250 mg (≥ 62.5 mmol/L) in men and ≥ 200 mg (≥ 50 mmol/L) in women. Hyperuricosuria was defined as urinary uric acid ≥ 800 mg (≥ 47.59 mmol/L) in men, while ≥ 750 mg (≥ 44.62 mmol/L) in women. Gouty diathesis was defined as urinary pH 5.5 or less. Hypocitraturia was defined as urinary citrate ≤ 450 mg (≤ 23.42 mmol/L) while hyperoxaluria was defined as urinary oxalate > 40 mg (> 444 μ mol/L). High urinary sodium was defined as > 150 mEq (> 150 mmol) in both genders.

Statistical analysis

Differences in clinical characteristics and metabolic diagnoses between the two temporally distinct groups were analyzed using the chi-squared test. An alpha level of < 0.05 was considered statistically significant. Statistical tests were performed using SPSS version 25.0.

Results

The study included 538 patients from two temporally distinct groups; Group A included 309 stone patients evaluated from 1988 to 1994, while Group B included 229 patients from 2007 to 2010. Table 1 describes the clinical characteristics of patients in both groups. There were significant differences in gender, age ($<$ or ≥ 50) and BMI classification between Group A and Group B ($p < 0.005$). From Group A to Group B,

female stone formers increased from 43.4% (134) to 55.9% (128) ($p = 0.004$). Patients 50 years and older also increased from 28.8 (89) to 46.7% (107) ($p < 0.001$). From Group A and Group B, there was also an increase in obese (BMI ≥ 30) patients, from 22 (68) to 35.4% (81) ($p = 0.003$). Correspondingly, the number of normal weight individuals (BMI < 25) decreased from 41.7 (129) to 36.2% (83).

Table 2 compares the urinary metabolic evaluations across all patients in Group A and Group B. Hypocitraturia across all stone formers increased from 46.0% (142) in Group A to 59.8% (137) in Group B, ($p = 0.001$). Hyperoxaluria was present in 23.3% (72) in Group A and 30.1% (69) in Group B, ($p = 0.07$). A comparison of metabolic evaluations by gender is presented in Table 3. In males, hyperoxaluria increased 32.0% over time (from 56 of 175) in Group A to 52.5% (53 of 101) in Group B ($p = 0.001$). Similarly, hypocitraturia increased in males from 44.0% (77) to 64.4% (65), ($p = 0.001$). There was no significant difference between both groups in urinary sulfate (median 0.91 ± 0.31 in group A vs 0.86 ± 0.38 g/day in group B; p -value = 0.24) or urinary phosphate (median 18 ± 8 in group A vs 17 ± 11 meq/day in group B; p -value = 0.44).

A comparison of Group A and Group B by BMI is described in Table 4. Of the obese patients, hypocitraturia was present in 39.7% (27 of 68) in Group A and 63.0% (51 of 81) in Group B ($p = 0.005$). However, this increase over time in hypocitraturia was not noted in individuals with normal BMI ($p = 0.465$). Hyperoxaluria was similar across both Group A and Group B in both the normal BMI and obese patients. When comparing younger (age < 50) and older adults (age ≥ 50) across Group A and Group B (Table 5), we found that hypocitraturia increased in younger adults from 46.8% in Group A to 61.5% in Group B, ($p = 0.009$); in older adults, hypocitraturia increased from 43.8 to 57.9%, ($p = 0.049$).

Discussion

In this study, we compared Ca kidney stone formers from 1988–1994 (Group A) to 2007–2010 (Group B) at a single institution, and found an increase in the number of female, obese and older stone formers. In the contemporary group, we also report increased hypocitraturia, which was particularly associated with obese individuals, and hyperoxaluria, which was significant in males.

In our study, the male:female ratio decreased from 1.3:1 to 0.8:1 from Group A to Group B, a finding consistent with data from regional and nationwide surveys [1,12–14]. In an analysis of the Nationwide Inpatient Sample, Scales et al. [5] determined that the male:female ratio decreased from 1.7:1 in 1997 to 1.3:1 in 2002. A recent report from the Mayo Clinic also showed that from 1984 to 2012, females aged 18–39 had the highest increase in incidence of stone formation in Olmstead County, Minnesota [15]. Diet and lifestyle have been implicated in this rise in female stone formation, though it remains unclear whether high-oxalate, high-calcium, or fatty diets predispose to stone formation [16]. Obesity in females, however, may pose a higher risk for stone formation compared to non-obese women, to a

Table 1. Clinical characteristics and epidemiological parameters across all patients.

	Group A: 1988–1994 (n = 309)	Group B: 2007–2010 (n = 229)	p-value
Gender			
Male	175 (56.6)	101 (44.1)	0.004
Female	134 (43.4)	128 (55.9)	
Age			
<50	220 (71.2)	122 (53.3)	<0.001
≥50	89 (28.8)	107 (46.7)	
BMI			
Normal (<25)	129 (41.7)	83 (36.2)	0.003
Overweight (25–29.9)	112 (36.2)	65 (28.4)	
Obese (≥30)	68 (22.0)	81 (35.4)	

Table 2. Metabolic abnormalities across all patients.

	Group A: 1988–1994 (n = 309)	Group B: 2007–2010 (n = 229)	p-value
Low volume	229 (74.1)	116 (50.7)	<0.001
Gouty diathesis	96 (31.1)	23 (10.0)	<0.001
Hypercalciuria	157 (50.8)	79 (34.5)	<0.001
Hyperuricosuria	104 (33.7)	39 (17.0)	<0.001
Hyperoxaluria	72 (23.3)	69 (30.1)	0.07
Hypocitraturia	142 (46.0)	137 (59.8)	0.001
High urine Na	203 (65.7)	129 (56.3)	0.027

Table 3. Comparison of males and females.

Females	Group A: 1988–1994 (n = 134)	Group B: 2007–2010 (n = 128)	p-value
Low volume	105 (78.4)	65 (50.8)	<0.001
Gouty diathesis	35 (26.1)	14 (10.9)	0.002
Hypercalciuria	54 (40.3)	36 (28.1)	0.038
Hyperuricosuria	29 (21.6)	6 (4.7)	<0.001
Hyperoxaluria	16 (11.9)	16 (12.5)	0.89
Hypocitraturia	65 (48.5)	72 (56.3)	0.21
High urine Na	67 (50.0)	56 (43.8)	0.311
Males	Group A: 1988–1994 (n = 175)	Group B: 2007–2010 (n = 101)	
Low volume	124 (70.9)	51 (50.5)	0.001
Gouty diathesis	61 (34.9)	9 (8.9)	<0.001
Hypercalciuria	103 (58.9)	43 (42.6)	0.009
Hyperuricosuria	75 (42.9)	33 (32.7)	0.095
Hyperoxaluria	56 (32.0)	53 (52.5)	0.001
Hypocitraturia	77 (44.0)	65 (64.4)	0.001
High urine Na	136 (77.7)	73 (72.3)	0.31

Table 4. Comparison by BMI.

Normal (BMI <25)	Group A: 1988–1994 (n = 129)	Group B: 2007–2010 (n = 83)	p-value
Low volume	95 (73.6)	35 (42.2)	<0.001
Gouty diathesis	26 (20.2)	5 (6.0)	0.004
Hypercalciuria	56 (43.4)	22 (26.5)	0.013
Hyperuricosuria	29 (22.5)	9 (10.8)	0.031
Hyperoxaluria	23 (17.8)	16 (19.3)	0.791
Hypocitraturia	68 (52.7)	48 (57.8)	0.465
High urine Na	67 (51.9)	30 (36.1)	0.024
Obese (BMI ≥ 30)	Group A: 1988–1994 (n = 68)	Group B: 2007–2010 (n = 81)	
Low volume	51 (75.0)	47 (56.6)	0.030
Gouty diathesis	32 (47.1)	12 (14.8)	<0.001
Hypercalciuria	39 (57.4)	36 (44.4)	0.116
Hyperuricosuria	37 (54.4)	18 (22.3)	0.001
Hyperoxaluria	27 (39.7)	32 (39.5)	0.980
Hypocitraturia	27 (39.7)	51 (63.0)	0.005
High urine Na	53 (77.9)	61 (75.3)	0.706

relatively greater degree than obesity in men. The relative risk (RR) of incident stones in obese vs normal weight men was 1.33, whereas in obese vs normal weight women the RR was 1.90–2.09 dependent on age [6]. Females also appear to

have different risk ratios of stone development based on hyperinsulinemia and hypertension, and other factors such as estrogen therapy in postmenopausal women and calcium and vitamin D supplementation [17].

Table 5. Comparison by age.

Age <50	Group A: 1988–1994 (n = 220)	Group B: 2007–2010 (n = 122)	p-value
Low volume	167 (75.9)	71 (58.2)	0.001
Gouty diathesis	64 (29.1)	7 (5.7)	<0.001
Hypercalciuria	111 (50.5)	42 (34.4)	0.004
Hyperuricosuria	79 (35.9)	24 (19.7)	0.002
Hyperoxaluria	48 (21.8)	33 (27.0)	0.276
Hypocitraturia	103 (46.8)	75 (61.5)	0.009
High urine Na	145 (65.9)	74 (60.7)	0.332
Age ≥50	Group A: 1988–1994 (n = 89)	Group B: 2007–2010 (n = 107)	
Low volume	62 (69.7)	45 (42.1)	<0.001
Gouty diathesis	32 (35.9)	16 (15.0)	0.001
Hypercalciuria	46 (51.7)	37 (34.6)	0.016
Hyperuricosuria	25 (28.1)	15 (14.0)	0.015
Hyperoxaluria	24 (27.0)	36 (33.6)	0.312
Hypocitraturia	39 (43.8)	62 (57.9)	0.049
High urine Na	58 (65.2)	55 (51.4)	0.052

In our study, we report an increase in the number of obese patients in the contemporary cohort, from 22 to 35%. The concomitant rise in obesity and stone prevalence is well documented [7]. Obesity has previously been associated with increased uric acid (UA) nephrolithiasis, acidic urine and urinary excretion of oxalates, calcium, sodium, phosphate and UA [18,19]. We did not detect a parallel increase in gouty diathesis in calcium stone formers over time, a finding consistent with other reports [14], suggesting other mechanisms for calcium stone formation in obese individuals may be involved. Decreased physical activity, high caloric intake and sedentary lifestyle may confer increased risk of Ca kidney stone formation in these obese individuals [20].

We also report an increase in older stone formers (age ≥50), from 29 to 47% ($p < 0.005$), consistent with prior reports [15,21]. Like obese individuals, older individuals have increased rates of acidic urine, promoting UA stone formation [22]. Older individuals also more frequently present with atypical stone pain or absence of pain [23], and the increased prevalence may be confounded in part due to increased utilization of abdominal imaging. In addition, some recent studies have suggested large increases in pediatric stone disease, particularly in obese adolescent girls, which warrants further investigation across the different age brackets [24].

The contemporary cohort was associated with increased rates of hypocitraturia, which was particularly associated with obesity. Hypocitraturia is a common metabolic abnormality present in 20–60% of stone formers [25]. Potassium citrate (Kcit) is given to increase urinary pH and restore citrate to normal levels [26]. Obese patients with hypocitraturia have been associated with decreased responsiveness to Kcit, requiring more frequent doses to maintain a normal citrate level. The mechanism underlying this increase in hypocitraturia, particularly in obese patients, is likely related to diet and lifestyle changes. The diet of obese patients may differ from non-obese patients, with greater animal protein intake and decreased citrus fruits, vegetables, and fiber, all promoting hypocitraturia. However, the underlying mechanisms between obesity and hypocitraturia are not fully elucidated.

We also describe an increase in hyperoxaluria in the contemporary cohort, which was significant in males. A recent

study reported that urinary oxalate excretion was also increased in calcium stone formers from 1980 to 2015 [14]. We recently demonstrated in a systematic review that hyperoxaluria has increased significantly over the past two decades, with the effect more prominent in Asian populations [27]. The mechanism underlying this rise in hyperoxaluria is likely multifactorial. Hyperoxaluria has been associated with obesity in large retrospective studies, although the mechanisms underlying this association are complex and require further investigation [28].

To our knowledge, this is the first study assessing temporal changes in metabolic stone risk factors in two large cohorts from two separate eras. However, the study is not devoid of limitations. First, this was a single center observational study of Ca kidney stone formers from two temporally distinct periods with potential for selection bias and confounders. Differences in medical care and lifestyle between the two time periods not captured by our measurements may influence the results. Finally, more comprehensive clinical information and further characterization of stone composition were not available for these patients. Our study therefore reports the temporal changes in 24-hour urine collections and metabolic diagnoses of stone formers across recent decades coinciding with the rise in stone prevalence, adding to the limited body of published data on this subject. The mechanisms underlying increased hyperoxaluria in male stone formers and hypocitraturia in obese Ca kidney stone formers ought to be further investigated in larger studies.

Conclusions

Kidney stone disease prevalence significantly increased in female, older, and obese patients. Hypocitraturia, particularly in obese patients, and hyperoxaluria in males also increased over time. Further studies using multi-center databases are warranted to further characterize the metabolic trends associated with the rise of stone formation.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or

national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. Informed consent was obtained from all individual participants included in the study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

Ramy F. Youssef: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. Jeremy W. Martin: Data collection or management, Data analysis, Manuscript writing/editing. Khashayar Sakhaee: Data collection or management, Data analysis, Manuscript writing/editing. John Poindexter: Protocol/project development, Data collection or management. Sharmin Dianatnejad: Management, Manuscript writing/editing. Charles D. Scales: Protocol/project development. Glenn M. Preminger: Protocol/project development. Michael E. Lipkin: Protocol/project development.

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