ORIGINAL ARTICLE

Trends in 24-hour Urine Parameters Based on Calcium Oxalate Monohydrate versus Calcium Oxalate Dihydrate State

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ABSTRACT

Introduction: Current American Urological Association guidelines suggest that a 24-h urine collection should be obtained in high-risk, 1st-time, and recurrent stone formers. Prior work suggests that urine chemistries can influence the morphology of calcium oxalate (CaOx) stone toward varying concentrations of the monohydrate (CaOx Monohydrate [COM]) or CaOx dihydrate (COD) crystal structure. We evaluate if stone composition in CaOx stone formers predicts 24 h urine results. **Methods:** We retrospectively reviewed stone analyses from the Beck Analysis laboratories database from January 1, 2002, to July 1, 2018. From 1001 patients, we identified 123 pure COM and 70 pure COD patients with 24-h urinalyses that could be paired with their stone analysis. Patients younger than 18 or with mixed or non-CaOx stone analyses were excluded. **Results:** COM patients were significantly older than COD (60.7 + 13.1 vs. 43.2 + 14.6; $P < 0.0001$) patients. On 24 h urine studies, COM patients had lower urinary calcium (174.9 + 108.0 vs. 288.2 + 127.3; $P < 0.0001$), higher urinary oxalate (45.1 + 21.8 vs. 36.7 +14.6; $P = 0.001$) and lower urinary pH (5.99 + 0.58 vs. 6.21 + 0.49; $P = 0.0062$) than COD patients. On multivariate analysis, COD patients showed significantly higher urinary calcium when compared to COM ($P < 0.0001$). Comparison of pCOM and pCOD patients showed correlation with hyperoxaluria (51.2% vs. 31.4% $P < 0.01$) and hypercalciuria (23.6% vs. 72.9% $P < 0.0001$), respectively. **Conclusions:** In patients with predominant or pure COD, in whom a 24-h urinalysis is not available, treatment of underlying hypercalciuria will likely aid in the prevention of further stone events.

Key words: Calcium oxalate stone disease, stone analysis, stone prevention

INTRODUCTION

In the United States, the prevalence of the stone disease is increasing.[1] The prevention of stone formation and decreasing the risk of stone recurrence is a critical step to reduce healthcare costs. Current guidelines from the American Urologic Association suggest that clinicians should perform additional metabolic testing, which includes two 24-h urine collections obtained on a random diet, in high-risk, or interested 1st-time stone formers.[2] This recommendation is in contrast to the European consensus that suggests a specific metabolic workup is necessary for only high-risk stone formers.[3] As previously stated, dietary and medical adjustments to prevent stone formation is important to improve patient well-being and cut medical costs. However, in specific cases, the prospect of making these adjustments without 24-h urine studies has been suggested; one example is with calcium oxalate (CaOx) stone disease.

It is well established that CaOx stones are the predominant stone type in the United States. In 1962, Herring discovered CaOx in approximately 80% of the stones analyzed.[4] In 2014, Lieske *et al*. demonstrated that CaOx stones are still by far the most common stone type by reporting that greater than two-thirds of the first stones collected from over 43,000 patients consisted of majority CaOx.[5] When present in stones, CaOx

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most commonly occurs as a mixture of CaOx monohydrate (COM) and/or CaOx dihydrate (COD). Although noticeably more rare,[6] pure COM and pure COD stones can also be encountered. The clinical cases associated with these stones in their pure states offer a unique opportunity to understand the underlying pathology leading to variations in CaOx stone formation.

The concept that urine chemistry may influence or at least correlate with the different crystal forms of CaOx is not novel. In 1955, Cottet and Vittu found that more than 60% of CaOx stone formers excreted >200 mg of calcium per day in their urine.[7] Hodgkinson and Pyrah (1958) validated these findings in a larger cohort, and in 1962, Murphy and Pyrah used microradiography to further suggest an influence of urine chemistries on the morphology of CaOx stones.[8,9] They found that less than a third of patients with striated (i.e., COM) stones demonstrated hypercalciuric states with 24-h calcium excretions exceeding 200 mg/d. By contrast, 71% of crystalline (i.e., COD) stone formers had hypercalciuria. More recently, Parent *et al*. (1999) and Daudon *et al*. (2016) demonstrated a strong correlation between hypercalciuria and predominantly (at least 60%) COD stones formers.[10,11] Furthermore, parent's group found that over 50% of the COM patients had hyperoxaluria in excess of 0.45 mmol/day, compared to only 12% of the COD group. These findings prompt the idea that a stone analysis alone, in CaOx stone disease, may be sufficient to initiate medical or dietary changes to prevent further stone formation.

We hypothesized that pure-COM stone formers would exhibit reduced prevalence and extent of hypercalciuria and pure-COD stone formers would demonstrate a significantly higher degree of hypercalciuria. To determine if and what specific physicochemical and metabolic conditions favor the formation and/or sustainment of the two different CaOx hydrates *in vivo*, it would be best to consider them in their purest forms. To best evaluate this hypothesis, we compared the 24-h urine collections of patients with pure COM stones to those with pure COD stones with the hopes of offering clinical value in terms of therapeutic strategies to CaOx urolithiasis.

METHODS

After Institutional Review Board approval, a retrospective review of patients with a 100% COD or COM stone analysis completed by Beck laboratories using infrared spectroscopy from January 1, 2002, to July 1, 2018, was completed. All stones were obtained after surgical stone extirpation at our institution. We identified 1001 CaOx stone patients, with 210 having pure COD and 791 having pure COM. Within this group, 139 pure COM patients and 79 pure COD patients had an associated 24-h urine study obtained after surgical treatment and before any recommendations or medical intervention. All 24-h urinalyses were completed by LitholinkTM. A comprehensive chart review of this cohort was completed to evaluate for comorbidities associated with stone disease. Following exclusion of both pediatric patients and patients with bilateral stones who had mixed- or non-CaOx stones in the other kidney, 123 patients with pure COM stones and 70 patients with pure COD stones were ultimately included for analysis. Means were compared using t-test and Chi-square. To simplify our analysis, we did exclude all patients with primary and enteric hyperoxaluria that would form whewellite Ic and Ie stone subtypes, as these are rarely encountered patients that are often managed with serial metabolic urinalyses.

RESULTS

Patient demographics and 24-h urine characteristics are reported in Table 1. Of the 123 COM patients, 65 (53%) were men, who were similar to the 70 COD patients in which 36 (51%) were men; $P = 0.88$. The COM patients were significantly older than the COD patients (mean 60.7 years vs. 43.2 years; $P < 0.0001$). Pertinent medical comorbidities within the cohort included: Primary hyperparathyroidism (2 COM; 3 COD); malabsorption syndromes including surgical bowel resection or diversion, bariatric surgery, or Crohn's disease (24 COM; 2 COD); medullary sponge kidney (4 COM; 0 COD); and anatomical anomalies including horseshoe, solitary, bifid collecting system, and ectopic kidney (9 COM; 2 COD). When considered independently, calcium excretion (174.9 ± 108.0 vs. 288.2 ± 127.3 mg/dL $P = 0.001$), urine pH (5.99 + 0.58 vs. 6.21 + 0.49; 0.006), uric acid excretion (0.58 + 0.23 vs. 0.65 + 0.24; $P = 0.028$), and magnesium excretion (97.1 + 46.2 vs. 109.9 + 40.9) were greater in the COD group, while oxalate excretion was greater in the COM (45.1 ± 21.8 36.7 ± 14.6 $P = 0.0016$) group. Among calculated parameters, urine calcium-to-creatinine ratio, calcium concentration, citrate concentration, calcium-to-oxalate molar ratio, and relative supersaturation rates of both CaOx and calcium phosphate were greater in the COD group. When all independent variables were taken into account, as effects in a general linearized model, age, calcium, sulfate, and urea nitrogen excretion were statistically different among the two groups. Figure 1 illustrates the significant difference in calcium excretion and the calcium-to-creatinine ratio between the two groups. When using the Ca/Cr ratio (>140) to delineate hypercalciuria, only 23.6% of patients in the COM versus 72.9% of the COD patients were hypercalciuric (Chi-square 45.675, $P < 0.0001$ – Table 2). Conversely, just over half of the COM patients were hyperoxaluric versus only 31.2% of patients in the COD group (Chi-square 7.218, $P = 0.0102$). Using multivariate analyses only 24 h calcium ($P = 0.00002$), patient age ($P = 0.00038$), and 24-h UUN ($P = 0.0017$) were significant effects. 24-h calcium is obviously higher in the COD patients, and they are quite a bit younger than those patients with pure COM stones [Table 1]. The UUN effect is

Table 1: All 24-hour urine biochemistry data (mean ± SD except for 'N,' 'Sex,' and 'Days b/w') from patients with pure COM or COD stones along with p-values from two-tailed independent samples t-tests assuming unequal variances as well as from a general linearized model using included variables as effects

Variable	Parameter	COM	COD	Two-tailed p-value	Adjusted multivariate p-value
Patient data	N	123	70		
	Sex (M/F)	65/58	36/34	0.8816	ns
	Age	60.7±13.1	43.2±14.6	**< 0.0001**	**0.0003**
	Days between stone analysis and 24hr Urine (IQ range)	-36 – 68 d	6 – 112.5 d	0.6188	ns
	BMI	31.8±9.80	29.3±8.18	0.0805	ns
24-hour urine collection	Volume (L/d)	1.92±0.80	1.70±0.80	0.0579	ns
	Calcium (mg/d) (mmol/d)	174.9±108.0 4.36±2.69	288.2±127.3 7.19±3.18	< 0.0001	< 0.0001
	Oxalate (mg/d) (mmol/d)	45.1±21.8 0.51±0.25	36.7±14.6 0.42±0.17	**0.0016**	ns
	Citrate (mg/d) (mmol/d)	604.3±380.8 3.15±1.98	708.9±393.6 3.69±2.05	0.0747	ns
	pH	5.99±0.58	6.21±0.49	**0.0062**	ns
	Uric Acid (g/d)	0.58±0.23	0.65±0.24	**0.0284**	ns
	Sodium (mmol/d)	180.2±77.3	174.9±77.7	0.6488	ns
	Potassium (mmol/d)	57.7±25.4	55.1±23.2	0.4718	ns
	Magnesium (mg/d)	97.1±46.2	109.9±40.9	**0.0475**	ns
	Phosphorus (g/d)	0.89±0.35	0.94±0.34	0.4075	ns
	Ammonium (mmol/d)	30.6±15.0	32.5±15.5	0.4253	ns
	Chloride (mmol/d)	173.4±74.2	160.4±69.4	0.2239	ns
	Sulfate (mmol/d)	33.3±16.3	37.3±15.3	0.0916	**0.0112**
	Urea Nitrogen (g/d)	9.93±4.10	9.52±3.59	0.4725	**0.0024**
	Creatinine (mg/d) (mmol/d)	1555.2±536.9 13.75±4.75	1585.7±617.9 14.02±5.46	0.7309	ns
Derived parameters	Ca/Cr (mg/d / g/d) (mmol/d / mmol/d)	115.8±72.3 0.33±0.20	193.1±94.6 0.54±0.27	**< 0.0001**	-
	CrCL (mL/min)	106.9±42.4	103.4±37.0	0.6317	-
	PCR (g/kg/d)	0.87±0.30	0.90±0.22	0.4907	-
	SS CaOx	6.83±3.60	10.0±4.40	**< 0.0001**	-
	SS CaP	0.85±0.76	2.18±1.22	**< 0.0001**	-
	SS UA	1.01±0.89	1.00±1.02	0.9967	-
	[Ca] (mmol/L)	2.46±1.50	4.89±2.31	**< 0.0001**	-
	[Ox] (mmol/L)	0.30±0.18	0.28±0.12	0.4038	-
	[Cit] (mmol/L)	1.82±1.21	2.58±1.89	**0.0030**	-
	[Ca]:[Ox]	10.2±7.25	18.4±8.48	**< 0.0001**	-

less obvious, but graphing 24-h UUN versus urine calcium showed that for any given value of calcium excretion, the COM patients had consistently higher UUN values than did the COD patients. This suggests a dietary difference between COM and COD patients in which the COM patients had higher protein intake for any given level of calcium excretion, a difference that would not be apparent by looking only at 24-h UUN.

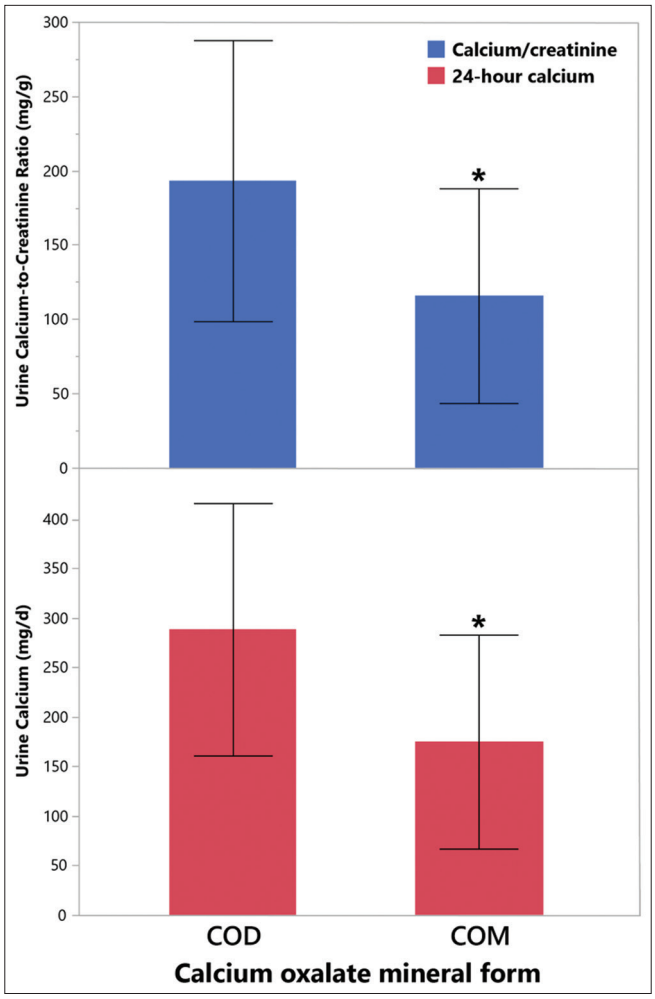

Figure 1: Comparison of hypercalciuria and hyperoxaluria between COD and COM patients. Asterisk indicates p<0.0001

Table 2: Prevalence of hypercalciuria versus hyperoxaluria in COM/COD stone formers

Variable	COM No. patients (%)	COD No. patients (%)	p-value
Hypercalciuria	29 (23.6)	51 (72.9)	**< 0.0001**
Hyperoxaluria	63 (51.2)	22 (31.4)	0.0102

DISCUSSION

Due to the recurrent nature of urolithiasis, stone prevention is paramount in reducing patient morbidity and health-care costs. A number of dietary changes and drug therapies have been empirically shown to reduce the likelihood of stone recurrence in CaOx stone formers and form the basis of current guidelines on medical stone disease management. Empiric recommendations such as increasing fluid intake to generate at least 2 L of urine per day, limiting dietary sodium intake to no more than 100 mEq/day, maintaining normal calcium intake, and instituting thiazide diuretic therapy have all been shown to reduce the risk of stone formation.[12-16] Such management decisions and recommendations have been instituted with and without the aid of detailed 24-h urine analyses. Detailed metabolic 24-h urine studies are beneficial in identifying metabolic derangements specific to the patient and are especially useful when coupled with a stone analysis. However, the results from a 24-h study can vary widely and are heavily subject to a patient's understanding of how to perform the study.[17,18] Furthermore, compliance is exceedingly low, even in high-risk stone formers. In 2014, Milose *et al*. demonstrated in a large series that only 7.4% of nearly 29,000 high-risk stone formers underwent a 24-h urine study within 6 months of their stone event. (cite: PubMed 24018242 - Milose JC, Kaufman SR, Hollenbeck BK, Wolf JS, Hollingsworth JM. Prevalence of 24-h urine collection in high-risk stone formers. J Urol. 2014;191(2):376-80.) On the other hand, a stone analysis, though not universal, is easily obtainable at the time of surgery and it represents an aggregate of crystal deposition over a prolonged period of time. This may provide a more comprehensive evaluation of the underlying pathology and local environment leading to stone formation.

Our data found that COD stone formers demonstrated significantly higher levels of 24-h calcium/creatinine excretion and were significantly more likely to have hypercalciuria compared to COM stone formers. These results support the theory that pure COD stone patients have high rates of hypercalciuria, which could be considered a reversible cause for their stone disease. By comparison, COM pure stone formers demonstrated hyperoxaluria in more than 50%, with only 23% having hypercalciuria and had higher urinary sulfate and urea nitrogen compared to COD stone formers. These data support the idea of environment and diet driving pure COM stone formation when patients with primary and enteric hyeroxaluria are excluded from the study. With such strong correlations in pure CaOx stone formers, our results support the concept of guiding metabolic stone prevention-based on a stone analysis in the absence or inability to obtain a valid 24 h urine study. Our results build on several previous studies. Pierratos *et al*. demonstrated similar findings when comparing the urine chemistries of 422 COM patients to those of 68 COD patients.[19] They showed that 24-h calcium excretion (278.54 mg/d vs. 171.13 mg/d) and the prevalence of hypercalciuria (54.4% vs. 18.25%) were significantly higher in the COD group. Galán *et al*. found that 71.6% of 102 COD patients were hypercalciuric based on their 24-h urines as opposed to just 34.6% of 153 COM patients.[20] The aforementioned two studies examined essentially "pure" stones as determined by X-ray powder diffraction and IR spectroscopy, respectively. Asplin *et al*. showed that, in men, the presence of any amount of COD (1–96%) in CaOx stones (determined by commercial laboratories) was associated with higher urine calcium excretion (315 mg/d, $n = 35$) when compared with 100% COM (222 mg/d, $n = 31$) stones. More

recently, Trinchieri *et al*. compared the 24-h urine parameters of 49 predominant (>60% by IR) COM stone formers and 32 predominant (>60% by IR) COD stone formers.[21] While only two of the COM stone analyses and none of the COD stone analyses were pure, they still found a significant difference in both urine calcium excretion (334 mg/d vs. 210 mg/d) and in the prevalence of hypercalciuria (50% vs. 16%). However, our study was the first to demonstrate the higher oxalate and dietary metabolites in COM stone formers as well as the higher urinary calcium content in COD stone formers. Based on such results, providers should consider treating presumed hypercalciuria in pure COD stone formers. This can be dietary recommendations such as improved fluid intake and reducing sodium consumption or initiating thiazide diuretic therapy – especially in patients with underlying osteopenia or osteoporosis. Predominant COM stone formers should consume a daily allowance of calcium to avoid excessive oxalate absorption, avoid overindulgence of oxalate rich foods, and limit high protein intake.

Our study is not without limitations. This is a retrospective review based on stone analyses showing CaOx disease. These data do not take into account patients with hypercalciuria with alternate or no stone composition. Despite the large cohort of CaOx stones analyzed by Beck labs, there were only a limited number with pure COM/COD stone compositions and a corresponding 24-h urine studies which could have resulted in selection bias. In addition, follow-up and stone treatment plans were limited and therefore we cannot comment on treatment response. Furthermore, it is possible that some stones sent for analysis represent a stone fragment and overestimate the purity in the stone analysis. In addition, although there are many publications outlining the variable pathophysiologies that lead to hyperoxaluria and hypercalciuria, this paper simply attempts to categorize urinary parameters that are associated with specific types of CaOx stones. The purpose of our study is not to supplant a 24 h study but to assist providers with a stone analysis in the focus of their stone prevention techniques. Finally, since most clinically encountered CaOx stones are mixed, direct applications of our study findings do have some limitation, however, in the absence of a metabolic urinalysis a stone analysis can offer insight into the underlying pathophysiology of an individual's stone disease. Despite these limitations, this study supports the theory of crystal formation as the result of a unique urinary milieu and supports the idea of empiric stone prevention therapy in patients with pure stone disease.

CONCLUSIONS

We conclude that in the setting where a 24-h urinalysis is not available, or a patient does not wish to perform a 24-h urine collection, consideration should be given to starting a thiazide diuretic to treat presumed underlying hypercalciuria in patients with pure COD stones. When a stone analysis suggests COM predominance, providers should counsel patients to maintain a normal calcium intake, avoid excessive intake of oxalate rick foods, and limit protein intake.

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