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# Variability in Stone Composition and Metabolic Correlation Between Kidneys in Patients with Bilateral Nephrolithiasis

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## Abstract

**Introduction:** To evaluate the clinical significance of discordant stone analyses in patients undergoing bilateral ureteroscopy.

**Methods:** A retrospective chart review was performed for all patients undergoing stone extraction with bilateral ureteroscopy at our institution in an aim to identify patients who had bilateral stone analysis and 24-hour urine chemistry data available. Stones were then classified based upon the dominant present (>50%). Twenty-four hour urinalysis results were reviewed and statistical analysis performed comparing discordant and concordant patient populations, assessing significant differences that would potentially influence clinical management.

**Results:** We identified 79 patients (158 renal units) who had bilateral stones removed at the time of ureteroscopy. The majority of stones were classified as calcium oxalate (CaOx) (60.1%) followed by calcium phosphate (CaP) (27.8%), brushite (5.1%), uric acid (UA) (4.4%) and cystine

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Conflict of Interest:

The following disclosures are listed as follows. JE Lingeman is a consultant for Boston Scientific and Lumenis. CA Dauw is a consultant for Boston Scientific. MS Borofsky is a consultant for Boston Scientific and Auris Health. AE Krambeck is a consultant for Boston Scientific and Lumenis. All other authors declare no conflict of interest.

Informed consent

Informed consent was performed at the time of enrollment into the prospective database for all included patients in this study.

(2.5%). Discrepancies in stone classifications were present 24% of the time. Evaluation of 24-hour urinalysis results demonstrated that patients with CaOx:CaP stone discordance compared to CaOx:CaOx concordant stone formers were more likely to have an elevated pH (p=0.02) and lower uric acid supersaturation (p=0.01).

**Conclusions:** Discrepancies in stone mineral content are common in patients with bilateral stone disease. A single stone analysis from one side in the setting of bilateral stone disease is insufficient for management of patients with bilateral renal stones, and may lead to mismanagement when this misrepresented information is utilized in addition to 24-hour urinalysis results. At least one stone analysis should be performed from both sides during a bilateral stone extraction procedure.

### Keywords

Nephrolithiasis; Calcium Oxalate; Calcium phosphate; Ureteroscopy; Discordance

## Introduction:

The current American Urological Association (AUA) guidelines recommend that stones be analyzed at least once when available.[1] There are no guidelines, however, discussing recommendations in obtaining a stone analysis when a bilateral stone procedure is performed. Furthermore, a recent review completed by the American College of Physicians (ACP) concluded that the current clinical trial evidence is insufficient to conclude that assessing stone composition, blood chemistry, or urine chemistry before or during pharmacologic or dietary management successfully prevents future stone events.[2] Despite the ACP conclusions, stone analysis and urine chemistries remain the cornerstone evaluations in the management of patients with nephrolithiasis and are recommended by the AUA.[3], [4]

To date, there is a limited amount of data surrounding discordant stone analysis when performing a simultaneous bilateral stone procedure.[4], [5] Stone analysis results as well as chemistries are utilized for the medical management of stone disease and could possibly be misrepresented if conflicting stone analysis results were present. The primary aim of this study was to review a cohort of bilateral stone forming patients in a prospectively collected ureteroscopy database to assess the prevalence of concordant and discordant stone compositions formed among renal units. Evaluations of both concordant and discordant patients who completed 24-hour urinalysis were performed to determine if there were significant differences between the two groups.

## Patients and Methods:

A prospectively collected IRB-approved ureteroscopy database was utilized and coupled with a chart review for patients undergoing synchronous bilateral ureteroscopy from 2013 to 2016 by a single surgeon (JEL) at a single hospital. All stones collected during the procedure were sent for analysis separately based on renal unit laterality. The stones were analyzed at a single stone analysis laboratory using all three of the following techniques for each test:

optical analysis, chemical analysis and Fourier transform infrared spectroscopy (Beck Analytical Laboratory, Indianapolis IN).

Stone composition per renal unit was classified by the dominant mineral present greater than fifty per cent. Stone compositions were identified as calcium oxalate (monohydrate or dihydrate) (CaOx), calcium phosphate (CaP), brushite, uric acid (UA), and cystine. An exception was made when brushite was present at any level. The renal unit was then classified as a brushite stone former.

Manual chart review was then completed for 24-hour urine study results (LithoLink, Labcorp). The study analyzed was the first 24-hour urine study completed for each patient, which at our institution is completed before the onset of medical stone management, and therefore represents the unaffected renal function. In first-time stone forming patients, this typically occurred after surgical treatment of the initial stone event, as is our routine practice. In patients whom we had previously treated for stone disease surgically, we included data from stone analysis obtained from the ureteroscopy during the study period (2013-2016) only. In these patients, we included the first 24-hour urine study obtained by the patient, which typically was obtained occurred the patient's first stone event, and therefore may have been up to several years prior to the study period. This represented the initial 24-hour urine study for the patient prior to intervention with any medical stone management.

Statistical analysis utilizing Student's t-test was performed evaluating differences in means comparing discordant and concordant patient populations, assessing significant differences in urine chemistries that would influence clinical management. All analyses were performed using IBM SPSS software, version 25 (Armonk, NY) with a significance level of $<0.05$.

## Results:

We identified 79 patients (158 renal units) who had bilateral stones removed at the time of ureteroscopy. The majority of stones were classified as calcium oxalate (CaOx) (60.1%) followed by CaP (27.8%), brushite (5.1%), uric acid (UA) (4.4%) and cystine (2.5%). Discrepancies in stone classifications between sides were present 24.1% of the time. Within the discordant stone results were the following analyses CaOx:CaP (63%), CaP: Brushite (32%), CaOx:UA (5%).

Among the 60 patients with concordant stone analyses, three patients (5%) had mixed UA and CaOx stones with all three having a predominance of UA. Also among patients with concordant stone analyses, 20 patients (33%) had both CaOx and CaP components. No patients of the concordant stones group had more than 2 types of stone present.

Among the 19 patients with discordant stone analyses, 17 patients (89%) had more than one type of stone present in the stone analysis from at least one side. Seventeen of these patients had a mixture of CaOx and CaP only in the stone on at least one side. Two (11%) patients among the discordant group had CaP and brushite only present in the stone on at least one side. Additionally, two of the discordant patients had 3 types of stone present on at least one side (both were a mixture of CaOx, CaP, and brushite). For both of these patients, the

brushite component was only present on one side. Ten (53%) patients among the discordant group had a pure stone on at least one side.

Overall, 62 patients (79%) within the cohort completed a 24-hour urinalysis (Table 1) with 84% of the discordant stone formers completing a 24-hour urinalysis. Evaluation of 24-hour urinalysis results demonstrated striking differences between those with conflicting and similar stone analysis results. Those patients with CaOx:CaP stone discordance compared to CaOx:CaOx concordant stone formers (Table 2) were more likely to have an elevated pH (p=0.02) and lower UA supersaturation (p=0.01).

## Discussion:

In a cohort of patients undergoing bilateral ureteroscopy, we identified a discordant stone analysis in 24% of cases. After evaluating the available 24-hour urinalysis results, we identified differences between CaOx:CaP and CaOx:CaOx stone formers with CaOx:CaP stone formers having an elevated pH and lower UA supersaturation than CaOx:CaOx stone formers. This difference in urinalysis results could lead a treating practitioner to patient mismanagement, both in the immediate post-operative management and long term if only a single stone analysis was performed for a given patient from a single side instead of both renal units. Specifically, practitioners not recognizing the presence of CaP stones may choose a treatment pathway that further alkalinizes the urine and potentially increases the risk CaP stones. Similarly, patients with an unrecognized UA stone component may not sufficiently recognize the importance of urinary alkalization.

Whether CaP stone or UA or other discordant stone disease is identified in a particular patient is due to several factors including the modality in which the stone is analyzed and the amount of stone submitted to the stone analysis laboratory. One of these is lab dependent while the other at the discretion of the treating urologist. While there exists no current “gold standard” for stone analysis, micro-CT is the most accurate but the lack of commercial availability makes other modalities including wet chemical analysis, infrared spectroscopy (FT-IR), x-ray diffraction more commonly used with variable success and determining components of mixed stones. Krambeck and colleagues assessed the accuracy of these variable stone composition analysis and found that in pure stones were more accurately analyzed than mixed stones, with significant discrepancies in mixed stone analysis results. Additionally, both the presence and absence of struvite in the stones was mischaracterized by multiple commercial labs. There was considerable variability with stones containing <50% apatite.[6] Given this potential for inaccuracies between labs and the finding of 24% of patients undergoing bilateral ureteroscopy having stone discordance between sides observed in the present study, the possibility of obtaining inaccurate information from a stone analysis can be high. Therefore, it would behoove urologists performing stone surgery to inquire as to the reputability of and techniques used by the analyzing facility so as to minimize the risk of receiving faulty information, in addition to ensuring that the bilateral stone specimens are sent for bilateral cases.

Literature regarding discordant stone formation is sparse. A retrospective review of fifty-nine patients by Kadlec et al found a 25% discordant stone formation rate, which is very

similar to our findings.[4] They likewise found an increase in CaP in the discordant stone group. A larger series of 126 patients by Zhou et al found that a larger fraction (48%) of patients undergoing either bilateral PCNL or ureteroscopy had discordant stone analyses. While our investigation was solely in ureteroscopy patients, Kadlec's and Zhou's investigations included patients undergoing PCNL as well and notably, 20% of patients in the Kadlec study had a partial or complete staghorn. Not surprisingly, struvite stone disease was identified in several of these patients. In those studies, no investigation into the effects on 24-hour urinalysis was made.

Nephrolithiasis has increased in prevalence over the past two decades and while men continue to have a greater incidence of stone disease, women have been narrowing the gender gap.[7], [8] A recent investigation into the temporal changes in stone composition and risk factors by Xu et al demonstrated a significant increase in the number of females with calcium stone disease from 24% to 42% over a period 35 years. There is likewise evidence of an increasing prevalence of calcium phosphate stone disease,[8] presenting a potential management conundrum in the CaOx:CaP discordant stone former.

One potential mechanism for discordant stones between kidneys is prior treatment with shock wave lithotripsy. This treatment option has been demonstrated histologically to induce histologic changes in the local treatment area of the kidney including hemorrhage, direct tubular damage, and scar formation.[9] In fact, changes in stone composition have been reported following shock wave lithotripsy in patients who form cystine stones.[10] Reinstatler et al reported that male gender and increasing number of treatments with prior shock wave lithotripsy were independently associated with the formation of non-cystine stone composition in a multi-institutional cohort of 125 patients who form cystine stones. This is especially interesting given the unique mechanism of cystine stone formation, and would suggest that prior treatment to a region of a kidney may locally induce changes that affect the stone composition from that papilla.

Medical management of stone disease in the recurrent stone former can be a challenge for the treating stone surgeon. After fluid and dietary recommendations pharmacologic intervention plays an important role at stone prevention. For the hypercalciuric calcium stone former, thiazide diuretics have been demonstrated in clinical trials to lower stone risk by reducing urinary calcium and are recommended by the current AUA guidelines.[3], [11], [12]. The mechanism of stone reduction is poorly understood but is likely due to reduced urine calcium coupled with a reduction in supersaturation.[13] Potassium citrate is frequently paired with thiazide therapy, both to reduce the likelihood of hypokalemia and to reduce stone recurrence rates.[14], [15] However, most investigations into the efficacy of citrate therapy on stone prevention has been in CaOx stone formers.[15] While AUA guidelines recommend addition of citrate in stone formers who are hypocitriuric and for those with persistent disease despite optimal management,[3] concerns remain in particular recurrent stone formers with CaP predominant stones. Patients with bilateral stones having multiple components or with discordant stone types may present the urologist with an even greater challenge for medical management given potential differences in treatment considerations for different stone types.

To date there is no randomized clinical evidence evaluating the effect of citrate therapy on CaP stone formation.[16], [17] In non-human studies of citrate therapy, potentially undesirable effects for CaP stone formation were noted including and increase in urinary pH and CaP supersaturation.[16] The concern for the managing urologist lies in the mechanism in which citrate decreases stone formation. While a portion of consumed citrate is filtered and complexes with calcium, thus decreasing stone formation, it also alkalinizes the urine via bicarbonate production after being metabolized by the liver and kidney.[18] This may result in a theoretical increase risk of CaP stone formation in particular in those with lower urine volumes and reduced urinary calcium.[18] A recent study by Dolzi et al[19] demonstrated that in hypercalciuric CaP stone formers, potassium citrate administration increased urine citrate and urine pH significantly compared to placebo and citric acid, but also increased brushite relative supersaturation ratio when measured with EQUIL2. While this study did not assess recurrent stone formation, it does leave the question of the relative risk and benefit of potassium citrate in these patients. To the urologist with a discordant CaOx:CaP stone former, the important information from a second stone analysis demonstrating predominant CaP stones would be particularly beneficial in recognizing the specific risk of worsening CaP supersaturation and potentially influence management depending on the provider's assessment of the clinical picture. Particularly in the case of our present study where 63% of patients with discordant stones had a predominance of CaOx on one side versus CaP on the opposite side, the management would require consideration of both stone types when deciding whether a medication such as potassium citrate would be appropriate. Given the lack of knowledge about specific recurrent stone risk in these patients who take or do not take potassium citrate, further study would provide tremendous benefit.

Our investigation is not without limitations. Approximately 80% of our patients completed a 24-hour urinalysis, which may not represent the urine chemistries of the entire cohort. Additionally, the small size of our cohort may not be generalizable to the population of stone formers regarding discordant stone analysis. Lastly, this was a retrospective review of a prospectively maintained database and thus is susceptible to selection bias.

## Conclusions:

Discrepancies in stone classifications are common in patients with bilateral stone disease. When metabolic evaluation was performed in these patients there were significant differences between discordant and concordant groups, especially CaOx only and CaOx:CaP stone formers. Thus, a single stone analysis in the setting of bilateral stone disease is insufficient and may lead to mismanagement when it is utilized in addition to 24-hour urinalysis results. Consideration should be made to include at least one stone analysis from each renal unit on future guidelines.

## Acknowledgments

Research involving human participants and/or animals

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. Institutional review board approval was approved at our institution (number 1010002243).

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**Table 1.**

Concordant and Discordant 24-hour urinalysis

| Discordant Classification 24-Hour Urinalysis | Mean Urine Volume (L) | Mean SS CaOx | Mean Urine Calcium mg/day | Mean Urine Oxalate mg/day | Mean Urine Citrate mg/day | Mean SS CaP | Mean 24 pH | Mean SS UA | Mean Urine UA g/day |
|---|---|---|---|---|---|---|---|---|---|
| **CaOx:CaP(n=10)** | 2.06 (1.08) | 8.49 (3.13) | 281 (109) | 40.1 (19.4) | 611 (262) | 2.39 (1.77) | 6.26 (0.44) | 0.579 (0.503) | 0.658 (0.251) |
| **CaP:Brushite(n= 5)** | 1.27 (0.37) | 8.60 (2.89) | 241 (96) | 30.2 (14.8) | 609 (309) | 2.24 (0.62) | 6.03 (0.25) | 1.06 (0.79) | 0.607 (0.158) |
| **CaOx:UA (n=1)** | 2.97 | 4.64 | 472 | 30.9 | 44.6 | 0.655 | 5.66 | 1.27 | 1.06 |
| **Concordant Stone Classification 24-Hour Urinalysis** | **Mean Urine Volume (L)** | **Mean SS CaOx** | **Mean Urine Calcium mg/day** | **Mean Urine Oxalate mg/day** | **Mean Urine Citrate mg/day** | **Mean SS CaP** | **Mean 24 pH** | **Mean SS UA** | **Mean Urine UA g/day** |
| **CaOx:CaOx (n=33)** | 1.78 (0.82) | 8.81 (3.44) | 233 (142) | 45.1 (19.8) | 568 (287) | 1.23 (1.01) | 5.88 (0.45) | 1.19 (0.87) | 0.612 (0.214) |
| **CaP:CaP (n=9)** | 2.02 (0.61) | 6.59 (2.63) | 245 (97) | 38.8 (9.6) | 319 (224) | 1.70 (0.94) | 6.44 (0.59) | 0.448 (0.412) | 0.637 (0.171) |
| **UA:UA (n=3)** | 1.90 (1.13) | 3.88 (1.25) | 166 (191) | 37.2 (5.6) | 461 (357) | 0.490 (0.362) | 5.83 (0.53) | 1.19 (0.94) | 0.779 (0.570) |

**Table 2 –**

24-Hour urinalysis results for CaOx:CaOx versus CaOx:CaP stone formers

| Stone Former | CaOx:CaOx N=33 | CaOx:CaP N=10 | P-value |
|---|---|---|---|
| **Mean Urine Volume, L (SD)** | 1.78 (0.82) | 2.06 (1.08) | 0.39 |
| **Mean SS CaOx (SD)** | 8.81 (3.44) | 8.49 (3.13) | 0.47 |
| **Mean U Calcium, mg/day (SD)** | 233 (142) | 281 (109) | 0.79 |
| **Mean U Oxalate, mg/day (SD)** | 45.1 (19.8) | 40.1 (19.4) | 0.49 |
| **Mean U Citrate, mg/day (SD)** | 568 (287) | 611 (262) | 0.68 |
| **Mean SS CaP, (SD)** | 1.24 (1.01) | 2.39 (1.77) | 0.08 |
| **Mean 24 pH, (SD)** | 5.88 (0.45) | 6.26 (0.44) | **0.02** |
| **Mean SS Uric Acid, (SD)** | 1.19 (0.87) | 0.579 (0.503) | **0.01** |
| **Mean Uric Acid, g/day (SD)** | 0.612 (0.214) | 0.658 (0.251) | 0.58 |