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24-Hour Urine Calcium Oxalate Supersaturation Risk Correlates with Computerized Tomography Volumetric Calcium Oxalate Stone Growth

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Study Need and Importance: For calcium oxalate (CaOx) stone formers, medical prevention is focused on lowering urinary supersaturation (SS) of CaOx to prevent crystallization and stone growth. Epidemiological and in vitro studies have shown a positive relationship between SS and stone growth. However, this link has not been well substantiated in vivo, eg does SS affect stone growth within a live kidney? Thus, we set out to measure percentage change in bilateral stone volume between 2 pre-surgical computerized tomography (CT) scans in CaOx (>80%) stone formers and to examine the effect on this growth by at least one 24-hour urine between the CT scans with SS CaOx and other factors.

What We Found: A total of 80 individuals met our criteria. Splitting the cohort into risk groups by SS CaOx, low (<5), medium (5–10) and high (>10), we found that median stone volume growth per year increased with increasing risk: 15%, 71% and 177%, respectively ($p < 0.001$; see figure). Likewise, a best fit of SS CaOx vs stone volume growth was moderately correlated (Spearman's rho = 0.53, $p < 0.001$). Of the 24-hour urine factors measured, and in a multivariate regression model, SS CaOx was the strongest independent predictor of stone volume growth.

Limitations: Our strict inclusion criteria led to a homogeneous population (pre-surgical surveillance) and small sample size, which may have obscured some effects. We also relied on one or two 24-hour urine collections as a snapshot of urine conditions for an average of 7 months growth between CTs, which may lead to variance due to short-term changes in SS CaOx.

Interpretation for Patient Care: Our study further corroborates the worth of SS CaOx in periodic 24-hour urines to monitor for stone activity. Despite intra-individual variations, in patients with active CaOx kidney stones, elevated SS CaOx (particularly above >10) is a moderate predictor of stone growth.

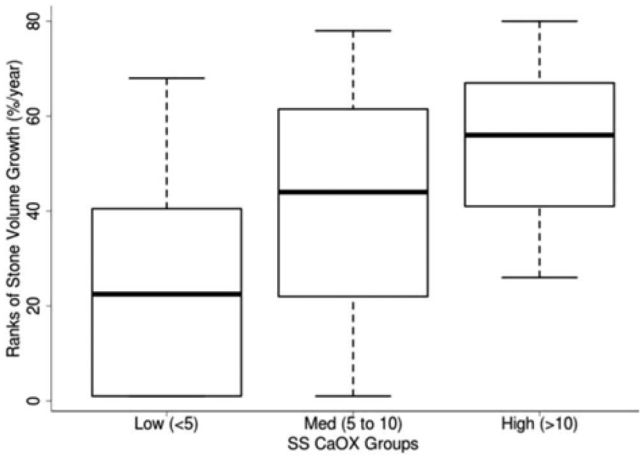

Figure. Annualized stone volume growth by SS CaOx groups (low, medium, high).

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24-Hour Urine Calcium Oxalate Supersaturation Risk Correlates with Computerized Tomography Volumetric Calcium Oxalate Stone Growth

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Purpose: In vitro experiments demonstrate calcium oxalate (CaOx) supersaturation (SS) drives CaOx nucleation and growth. We investigated the link between 24-hour urine SS CaOx and in vivo stone growth through a natural history, imaging study.

Materials and Methods: Using an institutional review board-approved database, we sought >80% CaOx stone formers who prior to stone intervention obtained 2 separate computerized tomography (CT) scans with at least one 24-hour urine collection between scans. Two blinded reviewers calculated bilateral 3-dimensional stone volume using the Visage 7® region of interest pen tool. CT volume difference was divided by time between scans, and SS CaOx was grouped into low (<5), medium (5–10) and high risk (>10). Statistical significance between groups was assessed by Kruskal-Wallis test.

Results: We identified 80 individuals with stone growth measured by 3-dimensional CT (mean ~7 months between studies). Inter-reviewer reliability of CT volume measurement was well correlated (0.98, Gwet's AC2), and an arbitrator was only needed in 13/160 (8%) cases. Median stone volume growth/year was 15%, 71% and 177% for low, medium and high risk groups, respectively ($p < 0.001$). Despite inter-individual variation, best fit of mean SS CaOx vs stone volume growth was moderately correlated (Spearman's rho = 0.53, $p < 0.001$).

Conclusions: In a population of pure CaOx stone formers, increased 24-hour SS CaOx risk was associated with increased in vivo stone growth. Further investigations using CT volumetric stone growth may allow for the noninvasive study of stone growth modulators, improved stone risk prediction and development of a kidney stone simulator.

Key Words: nephrolithiasis, calcium oxalate, kidney calculi, urine, tomography

Abbreviations and Acronyms

BMI = body mass index
CaP = calcium phosphate
Cit = citrate
CT = computerized tomography
HU = Hounsfield units
Ox = oxalate
SS = supersaturation

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Since the 1970s, the primary driver of urinary crystallization has been theorized to be the supersaturation (SS) of their associated urinary salts.[1] For calcium (Ca) oxalate (Ox) stone formers, medical prevention is focused on lowering urinary SS of CaOx in an aim to prevent crystallization and resultant stone growth.[2,3] Although a number of SS calculators exist, EQUIL2 is the most commonly used program to calculate SS from measured urinary solutes in a 24-hour collection.[4]

To establish this clinical guideline, the relationship between CaOx growth and SS CaOx was studied in a multifactorial approach. In vitro crystal kinetic work indicated that CaOx crystal growth was proportional to the square

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of CaOx SS.[5,6] Epidemiological studies then demonstrated that stone formers had higher SS than non-stone forming controls and that the likelihood of becoming a first-time stone former increased when stratified by SS risk and urine parameters.[7–9] Finally, prospective intervention trials revealed that lowering SS CaOx reduced clinical recurrences, defined as new stone formation or new symptoms from existing stones.[10–12]

Although these studies established the relationship between CaOx SS and the risk of becoming a stone former, this link has not been well substantiated in vivo—ie does SS affect CaOx stone growth within a live kidney? Increased stone volume growth between 2 separate computerized tomography (CT) scans has been shown to be predictive of future symptomatic stone events,[13] and automated stone volume calculations have recently been shown to be more accurate and reliable than hand measurements.[14,15] However, to our knowledge, the correlation of in vivo CT stone growth to CaOx SS has not previously been attempted. Therefore, the objective of this study was to accurately measure (using an automated tool) the percentage change in total stone volume between 2 pre-surgical CT scans in a population of CaOx stone formers and examine the effect of 24-hour urine CaOx SS (along with other measured urinary factors) on this growth rate.

MATERIALS AND METHODS

After obtaining institutional review board approval (IRB No. 201701160), we retrospectively queried our tertiary level institutional stone database to identify study participants. All patients in this database had either ureteroscopy or percutaneous nephrolithotomy between 2010 and 2017 with a resulting stone mineral composition analysis performed post-surgically of removed stone fragments. To be included in this particular study, participants were required to have 1) completed 2 separate CT scans before the stone surgery, 2) obtained at least one 24-hour urine collection between the 2 CT scans (no more than 2 years separation) and 3) demonstrated a mineral analysis ≥80% CaOx stone type (monohydrate or dihydrate).

Baseline Characteristics and Labs

All included participants had at least one 24-hour urinalysis performed through Litholink (Chicago, Illinois). Urinary components measured on a 24-hour total basis were total volume in liters, Ca, Ox, citrate (Cit), pH, uric acid, sodium, potassium, magnesium (Mg), phosphate, ammonium, chloride, sulfate, urine urea nitrogen, protein creatinine ratio and creatinine. Urinary SS for CaOx, calcium phosphate (CaP) and uric acid were precalculated by Litholink using the EQUIL2 program.[1] Based on commonly accepted ranges, SS CaOx groups were broken into low (<5), medium (5–10) and high risk (>10) groups. Arithmetic means with standard deviation were used for all patients who collected more than one 24-hour urine between CT studies. Procedures were considered "elective" when no emergency department visits were documented within 6 weeks of surgery and/or when there was no mention of flank pain at the clinic visit prior to surgery.

Stone Burden Measurement

Two reviewers, blinded to each other's findings, quantified total stone burden for all CT image series using previously described volumetric estimation methods.[13–15] To be included, all stones had to be within or superior to the ureteropelvic junction. Using CT bone windows, the stone perimeter within each CT image in the series was outlined by a semiautomated volume tool (region of interest pen tool; fig. 1) and tallied. Total CT stone burden was determined as the sum of all visible stone volume in mm^3 along with mean Hounsfield units (HU) for each stone. When the 2 reviewers' findings differed by more than 10%, an arbitrator (a board-certified urologist) served as a third reviewer.

Volumetric Stone Growth Quantification and Analysis

The difference in volumetric stone burden between CT 1 and CT 2 was considered stone growth rate and expressed as the percentage difference per year of volumetric stone

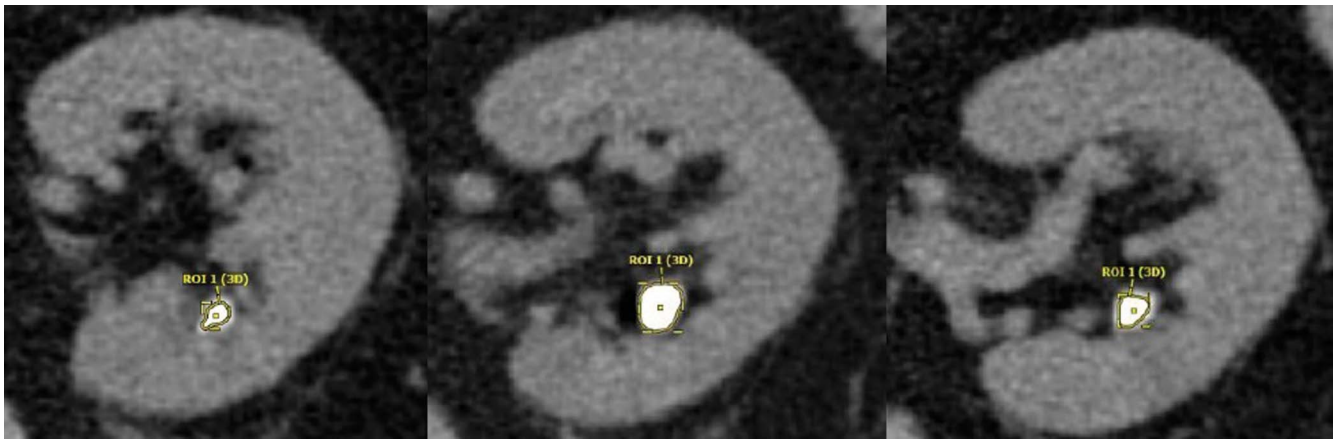

Figure 1. Example of region of interest pen tool semiautomated calculation of stone volume on multiple CT slices.

Table 1. *Clinical patient characteristics*

	Overall		Male		Female	
No. pts	80		42		38	
Demographics, comorbidities and stone-related parameters:						
Mean yrs age (SD)	57.1	(14.9)	59.3	(14.1)	54.7	(15.6)
Mean BMI (SD)	30.3	(8.3)	30.6	(8.6)	29.9	(8.1)
No. hypertension (%)	43	(54)	25	(60)	18	(47)
No. diabetes (%)	22	(28)	15	(36)	7	(18)
No. first-time stone former (%)	23	(29)	14	(33)	9	(24)
No. thiazide therapy (%)	10	(12.5)	5	(12)	5	(13.2)
No. allopurinol or citrate therapy (%)	7	(8.8)	5	(12)	2	(5.3)
Mean % CaOx mineral analysis (SD)	91.2	(8.6)	91.1	(8.4)	91.2	(9.0)
CT stone characteristics:						
CT 1:						
Median mm^3 stone vol (IQR)	413	(859)	706	(1,846)*	236	(447)*
Mean No. stones (SD)	2.6	(1.8)	2.5	(1.7)	2.7	(2.0)
Mean stone HU (SD)	505	(163)	555	(178)*	450	(125)*
CT 2:						
Median mm^3 stone vol (IQR)	505	(1,115)	959	(2,153)*	354	(498)*
Mean No. stones (SD)	2.9	(2.0)	2.9	(1.8)	2.9	(2.2)
Mean stone HU (SD)	551	(153)	580	(162)	518	(136)
Mean 24-hr urine parameters (SD):						
Collections	1.9	(0.4)	1.9	(0.5)	1.9	(0.4)
SS CaOx	7.2	(3.7)	6.7	(3.3)	7.9	(4.2)
Vol (L)	1.9	(0.9)	2.1	(0.9)*	1.7	(0.8)*
Ca (mg)	200	(136)	203	(155)	196	(113)
Ox (mg)	39.1	(18)	43.1	(20)*	34.6	(15)*
SS urinalysis	0.99	(0.87)	1.05	(0.92)	0.92	(0.81)
pH	6.00	(0.55)	5.93	(0.59)	6.07	(0.50)

* $p < 0.05$ between male, female by Mann-Whitney U test.

burden using the method of Patel et al.[15] Because in vitro CaOx stone growth is dependent on surface area,[16] we used percentage instead of absolute difference in volume to allow equal comparison regardless of initial stones size. The equation used was:

$$\text{Stone Volume Growth (\%/year)} = \left(\frac{\text{Total Volume}_{\text{2nd CT}} - \text{Total Volume}_{\text{1st CT}}}{\text{Total Volume}_{\text{1st CT}} \times (\text{Time}_{\text{2nd CT}} - \text{Time}_{\text{1st CT}})}\right) \times 100$$

To account for small errors in volume measurement, patients with ±5% absolute stone volume change between the 2 CT scans were considered as having "no growth." We excluded all individuals with >5% negative stone growth rates, as this degree of negative growth implied stone passage. To assess the independent association between SS CaOx and stone volume growth (natural log %/year), we created a multivariate generalized linear regression model and adjusted for age, gender, body mass index (BMI), diabetes, hypertension, recurrent stone and medical therapy.

Statistical Analysis

All analyses were performed using the free software program R™ version 3.6.3. Inter-reviewer reliability was assessed by Gwet's AC2 test. For normally distributed data, differences were quantified using Student's t-test. For nonnormally distributed data, associations were quantified by Spearman's correlation, and differences by Mann-Whitney U test and Kruskal-Wallis test.

RESULTS

We identified 368 patients (197 male, 171 female) in our database with ≥80% CaOx stone mineral content post-procedure. Of these, 94 fit study inclusion criteria. We excluded 1 individual who was an extreme stone growth outlier and 13 others who had >5% negative growth (stone passage), leaving 80 (42 male, 38 female) with positive or zero stone growth between the 2 pre-surgical CT scans. The baseline clinical characteristics of study participants are given in table 1. Most of cohort (~70%) were repeat stone formers on surveillance prior to kidney stone intervention with comorbidities including obesity (mean BMI >30), hypertension (56%) and diabetes (28%; table 1). There were 16 individuals (20%) on medications associated with lowered kidney stone risk. Ten individuals (5 male, 5 female) were on 25 mg hydrochlorothiazide daily, mainly for its antihypertensive properties. Four males were on 100 mg allopurinol for gout, and 3 patients (1 male, 2 female) were on a Cit medication (1 sodium Cit, 2 potassium Cit) for kidney stone history. We found no difference in stone volume growth between patients on/not on these medications ($p = 0.83$). Splitting the total cohort by gender, males had greater baseline and followup stone volume (~500 mm^3; $p < 0.001$) as well as greater 24-hour urine volume (~0.4 L; $p < 0.05$) and 24-hour oxalate (~9 mg; $p < 0.05$) than female stone formers. Mean±SD time between CT studies was 7.0±5.4 months, and time to stone intervention after CT 2 was 2.9±6 months. Most 24-hour collections (67/80, 86%) were done after the midpoint between CT 1 and CT 2, and the majority of participants (74/80, 91%) collected 2 specimens.

When stratified by SS CaOx risk, median stone volume growth was 15%, 71% and 177% for low (24 patients), medium (39) and high risk (17) groups, respectively ($p < 0.001$), a finding that remained

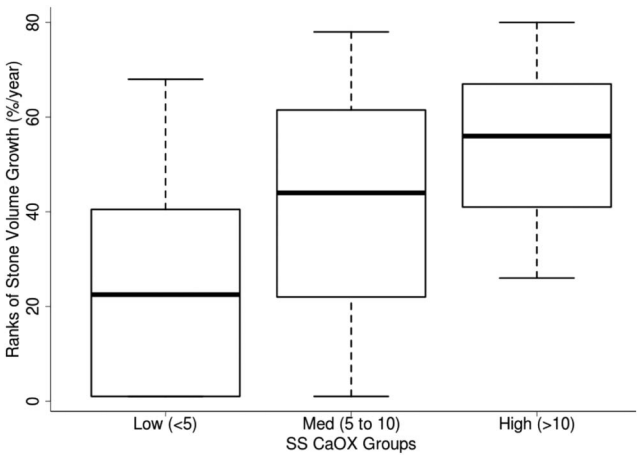

Figure 2. Annualized stone volume growth by SS CaOx groups (low, medium, high) for total cohort. Statistically significant differences were noted when %/year was plotted by increasing risk group (p for trend = 0.02).

Table 2. *Rank correlation for 24-hour urine parameters (continuous) vs stone volume growth (%/year)*

	Total	Male	Female
No. pts	80	42	38
SS CaOX	0.53*	0.41*	0.61*
SS CaP	0.46*	0.33*	0.54*
Ca^{2+} (mg/day)	0.38*	0.51*	0.25
Mg^{2+} (mg/day)	0.21	0.38*	0.03
Ox^{2-} (mg/day)	0.19	0.44*	-0.06
Cit^{3-} (mg/day)	0.11	0.31*	-0.17
Vol (L/day)	-0.10	0.25	-0.42*

* $p < 0.05$. Only parameters with at least 1 significant correlation in group are displayed.

significant when stone volume growth was annualized (p for trend = 0.02; fig. 2). Stone volume and urinary characteristics of these subgroups showed that individuals in the high SS CaOx group had significantly smaller CT 1 and CT 2 stone volumes, more ureteroscopic procedures and lower urine volumes than the other groups (table 2). When gender was then stratified by risk group, females had significant grouped differences ($p < 0.01$) while males did not ($p = 0.09$). Stone growth was most strongly correlated to SS CaOx (Spearman's rho = 0.53, $p < 0.001$; table 3) followed by SS CaP (0.46, $p < 0.01$) and 24-hour urine Ca (0.38, $p < 0.05$). Finally, SS CaOx was the only independent variable associated with statistically significant stone growth in our adjusted, linear regression model (supplementary table, https://www.jurology.com).

Scatterplots of these variables demonstrate their complexity in regard to gender. For the male cohort, the strongest positive correlate to stone growth was 24-hour urine Ca, followed by Ox, SS CaOx, Mg and Cit in descending order (fig. 3). Increasing urine volume was not correlated to decreased stone growth in males. Females had the strongest positive correlation for SS CaOx, while increasing 24-hour urine volume was negatively correlated with stone volume growth (fig. 3). Finally, we compared variables of individuals without growth (15 patients; 10 male, 5 female) to those with stone volume growth (65). The "no stone growth" group had lower SS CaOx (4.2 vs 7.6, $p < 0.001$) and 24-hour urine Ca (111 vs 194 mg per day, $p < 0.01$) than individuals with stone growth, but not urine volume ($p = 0.28$; data not shown).

DISCUSSION

The long held clinical dictum in patients who are actively forming kidney stones has been to measure 24-hour urinary SS and then attempt to drive it as low as possible. This maxim held true in clinical prospective trials, such as the large 2002 dietary intervention trial[10] or the 1996 water intervention trial,[11] which demonstrated that patients who form fewer new stones or have fewer stone symptoms will have lower urine mineral supersaturations. The converse, that high SS drives in vivo stone growth, is much more difficult to prove since stone former phenotypes vary greatly and stone measurements using plain x-ray or ultrasound are imprecise. In an attempt to control for all these previous inaccuracies, we selected a tight stone phenotype (>80% calcium oxalate mineral of the stone eventually removed) and used a semiquantitative, readily available application in our image viewing software to calculate highly accurate stone volumes. In this population of obese southern U.S. citizens on minimal medical stone management, increased 24-hour urine SS CaOx had a moderate association with increased CT volumetric stone growth over time. This finding was supported by 3 different yet complementary data methodologies: SS as a continuous variable, SS stratification by risk groups and SS between groups with or without stone volume growth. SS CaOx was also identified as the most important risk factor for increased in vivo stone growth across genders, surpassing that of SS CaP.

Table 3. *Stone volume and urine characteristics stratified by SS CaOx risk group*

	Low SS Risk	Medium SS Risk	High SS Risk	p Value*
No. pts	24	39	17	
CT 1 median stone vol (IQR)	661 (2,591)	416 (853)	102 (384)	0.009
CT 2 median stone vol (IQR)	859 (3,090)	500 (994)	251 (742)	0.04
Median % change in stone vol (IQR)	15.3 (51)	70.8 (237)	176.6 (292)	<0.001
No. percutaneous nephrolithotomy procedure/total No. (%)	12/24 (50)	8/39 (21)	1/17 (6)	0.003
No. elective surgery/ total No. (%)	17/24 (71)	25/39 (64)	7/17 (41)	0.14
Mean L 24-hr urine vol (SD)	2.5 (0.7)	1.9 (0.8)	1.2 (0.5)	<0.001
Mean mg 24-hr urine calcium (SD)	133 (95)	229 (159)	227 (92)	0.15
Mean mg 24-hr urine oxalate (SD)	35.3 (10.8)	42.3 (23.1)	36.9 (13.5)	0.29
Mean mg 24-hr urine citrate (SD)	438 (303)	455 (287)	598 (426)	0.25

* p for trend calculated by Kruskal-Wallis test (medians), chi-square (categorical) and ANOVA (means).

As figure 3 implies, there was considerable interindividual variation in growth rates when SS CaOx was plotted alone. At least in our population, this prevents the use of SS CaOx as a sole predictive tool for stone growth. This finding was expected, since a 24-hour collection is a snapshot of a lifestyle and dietary routine while the CT images reflect months of growth within the urinary milieu. Thus, our data reinforce the fact that SS CaOx is just 1 piece of a larger stone growth puzzle. Variations in daily peak excretion or the presence of unmeasured factors, such as urinary proteins or lipids (which have been

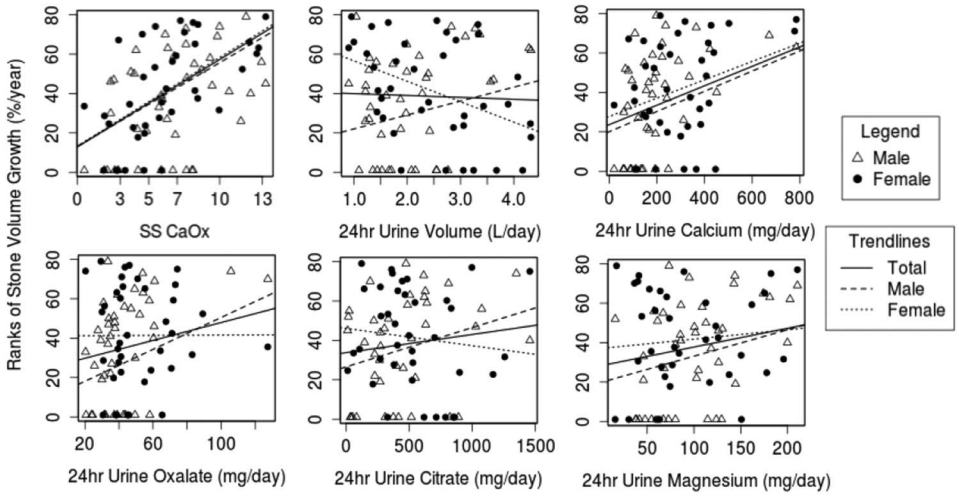

Figure 3. Mean 24-hour urine parameters plotted against stone volume growth rank (%/year) and stratified by gender using symbols and trendlines. Parameters displayed are significant in at least 1 group (total, male or female).

shown in vitro to affect stone growth independent of absolute SS CaOx[3,17]), are likely other parts of this puzzle.

There were significant gender differences in 24-hour urine parameters and stone volume growth. Of the measured urinary analytes stratified by male gender, increased urinary ions (primarily 24-hour urine calcium but also oxalate, magnesium and citrate) and to some extent increased urine volume contributed to stone growth in males. These findings are somewhat surprising, since urine volume and urinary magnesium/citrate are considered inhibitors of stone growth. More males in this subset may have been needed to tease out these differences further. We also did not attempt to link stone growth to papillary plaques or tubular plugs in this population, but this is certainly another reasonable explanation for this finding given their association with hypercalciuria.[18] Finally, perhaps calcium and oxalate ions superseded all other variables in our male population through some other physiological mechanism of stone formation that was not completely captured by SS CaOx. Unlike males, increased urine volume in our female cohort was correlated to decreased stone growth, while SS CaOx was the continuous variable most strongly tied to stone growth. Higher urinary citrate was also negatively correlated to stone growth, although not with statistical significance. In fact, 24-hour variables in our female cohort behaved almost exactly as we would have hypothesized, supporting other published 24-hour studies regarding gender and stone risk.[8]

There are limitations in our study methods, which could have altered association strengths. First, our homogeneous patient population and strict inclusion criteria (2 CT scans, a 24-hour urine and an intervention with narrow stone phenotype) led to a small sample size, potentially obscuring relationships that may be seen in larger populations. Second, Nayan et al (2012) showed that individual parameters on consecutive 24-hour urine collections can differ as much as 48%.[19] Although they did not report SS, our data corroborate their findings, demonstrating coefficient of variance for SS CaOx=0.51 in the 74 individuals who collected back-to-back urines. Finally, we chose to compare absolute SS CaOx between patients rather than relative SS CaOx, or the absolute change represented as a percentage of the earlier value. Ferraro et al (2018) looked at previous trial data and showed that short-term changes in relative SS CaOx predicted new stones (by ultrasound or plain x-ray) or new stone symptoms.[12] Rodgers reported that relative SS CaOx has higher diagnostic worth when comparing values between individuals, as each individual may have a different threshold value for stone nucleation and growth compared to entire group values.[17] This is intuitive and aligns well with our data showing that CT stone growth risk correlated best when examined by SS CaOx risk (high, medium, low), not SS as a continuous variable. Perhaps the SS CaOx number itself is less important than the range in which it sits and/or its relative change from previous values. This topic requires more investigation in the future.

CONCLUSIONS

In patients with active CaOx kidney stones, elevated SS CaOx (particularly >10) is a moderate predictor of kidney stone growth. This finding supports both the laboratory principles that drive stone formation as well as the AUA (American Urological Association) guideline on the medical

management of kidney stones, which recommends periodic 24-hour urine collections to monitor for stone activity, patient adherence and metabolic response.[20] Despite intra and inter-individual variations in 24-hour urine parameters, these data lay the initial foundation for stone growth predictive models and the groundwork for future kidney stone simulators.

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EDITORIAL COMMENT

While management of calcium oxalate supersaturation has been a cornerstone of medical stone prevention for almost half a century, there remain unanswered questions surrounding the utility of this endeavor. Studies have previously shown a connection between SS CaOx and in vitro CaOx crystal growth as well as the relationship between SS CaOx reduction and stone recurrence rates (present study and reference 12 in article). This study attempts to fill a gap in the literature regarding the effect of SS CaOx on in vivo stone growth by comparing changes in stone volume on successive CT scans to SS CaOx on intervening 24-hour urine collections. It is encouraging to see that, through multiple analytical methods, SS CaOx appears to track well with observed stone growth, suggesting that maintaining a lower SS CaOx may protect against an increase in stone volume over time.

There are a few surprising findings within this study that may require additional study or clarification in the future. Namely, the effects of urine volume, citrate and magnesium on stone growth seen in this study appear counterintuitive when considering prior data. Importantly, unlike most literature in this space, this manuscript utilizes percent change in stone volume over time, which may describe a particular category of stone growth and whose clinical relevance is not assured.

As dietary management has previously been correlated with stone risk reduction (reference 10 in article), it is also important to note that the 24-hour urine collections in this study act as snapshots and do not account for prevention measures that may have been undertaken during the study period. Despite these limitations, a more nuanced understanding of SS CaOx over time will clearly inform a deeper knowledge surrounding its relationship to stone growth; in the meantime, this study is a substantial further indication that urinary supersaturations are an important clinical outcome for kidney stone prevention.

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