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Clinical and Metabolic Correlates of Pure Stone Subtypes

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ABSTRACT:

Background:

There are multiple stone types, each forming under different urinary conditions. We compared clinical and metabolic findings in pure stone formers to understand if there are consistent factors that differentiate these groups in terms of underlying etiology and potential for empiric treatment.

Materials and Methods:

Pure SFs based on infrared spectroscopic analysis of stones obtained at our institution between 01/2002 and 07/2018 with a corresponding 24-hour urinalysis were retrospectively evaluated.

Results:

121 apatite, 54 brushite, 50 calcium oxalate dihydrate, 104 calcium oxalate monohydrate, and 82 uric acid patients were analyzed. Apatite, brushite, and calcium oxalate dihydrate patients were younger than calcium oxalate monohydrate and uric acid patients. Uric acid patients had the highest male predominance (76.8%), while apatite patients were predominantly female (80.2%). Uric acid was most associated with diabetes mellitus (45.3%), and calcium oxalate monohydrate with cardiovascular disease (27.2%) and malabsorptive gastrointestinal conditions (19.2%). Brushite patients had the highest prevalence of primary hyperparathyroidism (17%). Apatite, brushite, and calcium oxalate dihydrate patients demonstrated high rates of hypercalciuria (66.1%, 79.6%, 82%). Apatite and brushite patients had the highest urinary pH. Apatite patients exhibited the highest rate of hypocitraturia while calcium oxalate dihydrate patients exhibited the lowest (55.4%, 30%). Calcium oxalate monohydrate patients had the highest rate of hyperoxaluria (51.9%). Uric acid patients had the lowest urinary pH. There were no observable differences in the rates of hyperuricosuria or hypernatriuria.

Conclusions:

These results demonstrate that pure stone composition correlates with certain urinary and clinical characteristics. This data can help guide empiric clinical decision-making.

Introduction:

In the United States, the prevalence of kidney stones is estimated at 8.8%.[1] Stone disease generates more than a million emergency department visits per year with a reported 70,000 annual stone-related surgical procedures performed.[2] Recurrence rates after the initial stone event are estimated to be approximately 50% at 10 years.[3] Recurrence rates have been shown to differ based on stone composition.[4] Although there have been nearly 100 different components identified in human urinary calculi and at least 25 unique pure stone types, the most commonly encountered compositions are: calcium oxalate (CaOx) monohydrate (COM) or dihydrate (COD), calcium phosphate (CaP) as apatite (AP) or brushite (BRU), and uric acid (UA).[5,6]

A continued effort to promote the medical management and prevention of kidney stones is imperative to reduce the cost burden associated with surgical and recurrent stone disease. At the center of metabolic stone prevention are specific dietary and medical therapies, which are uniquely effective to a patient based on certain metabolic abnormalities, urinary environments, and stone compositions. A recent publication demonstrated that stone formers (SFs) with predominant (≥ 80%) COM stones had higher incidences of hyperoxaluria and hypocitraturia while COD SFs were more likely to be hypercalciuric.[7] In addition to COM and COD, other pure SFs likely vary with respect to their urinary characteristics; therefore, establishing associated metabolic abnormalities with each stone type could potentially advance our understanding of how these stones form and how they could be prevented. Such information would be valuable to help guide empiric management in patients who cannot or are unwilling to perform a 24-hour urine evaluation. We compared metabolic and clinical findings in pure AP, BRU, COD, COM, and UA SFs in an attempt to establish characteristics that may contribute to their specific stone formation and guide the prevention of further stones.

Patients and Methods:

After IRB approval **(number: 1901326951)**, we retrospectively queried our clinical data registry and identified pure SFs based on infrared spectroscopic analysis (Beck Analytical Services, Greenwood, IN) of renal or ureteral stones obtained at our institution

via endoscopic extraction or spontaneous passage between 01/2002 and 07/2018. Pure was defined as 100% of a single stone subtype. We initially identified 3,760 patients with a 100% AP (1,391), BRU (436), COD (210), COM (791), or UA (932) stone analysis. Among these patients, only those who had a 24-hour urine evaluation (Litholink/LabCorp, Itasca, IL) within a year of the stone analysis were included. Creatinine-per-kilogram (Cr/Kg) in the 24-hour urine sample had to be within a pre-specified range of 15-25 mg/kg to ensure adequate collections. Patients were also excluded if they were younger than 18, initiated medical or dietary changes intended to prevent stone formation prior to their 24-hour urine collection, or had a bowel-containing urinary diversion. For seven patients with multiple stone events as determined by chart review or our pure stone database, we selected the first recorded 100% stone analysis that also had an associated metabolic urine study in our 24-hour urine database.

Clinical characteristics including basic demographic information, comorbidities, and pregnancy within 6 months of stone or urine collection were recorded and analyzed. Statistical analysis was performed using JMP Pro (SAS Institute Inc., Cary, NC) and included: 1. Multivariate analysis using a nominal logistic fit model predicting stone type from measured 24-hour urine parameters, sex, age, and BMI; 2. One-way ANOVA and post-hoc Tukey-Kramer HSD tests demonstrating within group differences for interval variables; and 3. Fisher's exact and analysis of means for proportions tests demonstrating within group differences for nominal variables. For these group comparisons, we employed a significance factor of $p < 0.05$.

Results:

After meeting all inclusion and exclusion criteria, 411 pure SFs were analyzed – 121 AP, 54 BRU, 50 COD, 104 COM, and 82 UA SFs (Table 1). Demographically, AP, BRU, and COD SFs were significantly younger than COM and UA SFs (Tukey: $p < 0.0001$ except UA-BRU pair [$p=0.0098$]). There were no observable differences in sex amongst BRU, COD, or COM SFs (55.6%, 58%, and 53.8% male, respectively); however, UA SFs had the highest male predominance (76.8%, $p < 0.0001$), while AP SFs were predominantly female (80.2%, $p < 0.0001$). UA SFs had significantly higher BMI than each of the other groups except COM (Tukey: $p < 0.0001$ except UA-BRU [$p=0.0005$], UA-COD [$p=0.0007$], and AP-COM

[*p*=0.0029] pairs). For the entire cohort, 24-hour urine collections occurred, on average, 20 days after the corresponding stone event (interquartile range: -28 – 59; Tukey: no significant pairs). There was also no observable difference in mean Cr/Kg between the groups.

Certain medical comorbidities differed amongst the five groups of SFs, based on univariate analysis (Table 1). COM SFs were significantly more likely to have a history of Crohn disease, bariatric surgery, or short bowel syndrome; UA SFs were the only patients in our cohort to have an end ileostomy in place; and BRU SFs had a significantly higher prevalence of primary hyperparathyroidism. COM and UA SFs were more likely to have hypertension and dyslipidemia. UA SFs had the highest proportion of patients with diabetes mellitus, and COM SFs had the highest rates of cardiovascular disease and gout.

Comparison of 24-hour urine results between the five groups is summarized in Table 2 and illustrated in Figure 1. Among independent parameters, univariate analysis revealed significant differences in all factors except sodium, magnesium, and ammonium excretion. Multivariate analysis revealed sex, age, pH, and 24-hour calcium, oxalate, urea nitrogen, potassium, and citrate excretion to be independent predictors of stone type. No changes in outcomes or effect significance were seen when creatinine excretion and number of days between urine and stone analysis were included, so we removed these variables from our multivariate model. AP, BRU, and COD SFs demonstrated greater calcium excretion than COM and UA SFs (Tukey: $p < 0.0001$ for all significant pairs except UA-COM [*p*=0.0027] and AP-BRU [*p*=0.0306]). AP and BRU SFs also had higher urinary pH than the other groups (Tukey: $p < 0.0001$ for all significant pairs except BRU-COD [*p*=0.0038], AP-COD [*p*=0.0006], and COD-COM [*p*=0.0347]). AP SFs demonstrated significantly lower citrate excretion than COD SFs (Tukey: *p*=0.0043). COM SFs demonstrated greater oxalate excretion than all of the other groups except UA (Tukey: $p < 0.0001$ for all significant pairs except BRU-COM [*p*=0.0286] and COD-COM [*p*=0.0322]). UA SFs demonstrated normal uric acid excretion but had lower urinary pH, higher urea nitrogen excretion, and the highest relative supersaturation rates of UA compared to the other stone types (Tukey: $p < 0.0001$ for these UA pairs). For potassium excretion, the only

stone type pair with a statistically significant difference was COD and UA (Tukey: p=0.0247).

Discussion:

Despite the complexity of stone formation, we have a limited number of lifestyle and medical interventions scientifically proven to prevent kidney stones. The majority of stone prevention relies on 24-hour urine evaluations and as such, guidelines in both Europe and the United States have integrated the use of these studies into their treatment algorithms.[8,9] While a metabolic urine study represents a patient's urinary environment over a 24-hour period, a stone is the aggregation of crystal deposition over a prolonged period of time. Fortunately, in the United States, 24-hour urine-based stone risk assessments are universally available and easily obtainable; however, this is not the case throughout the world,[7,10] and even if a test is provided to a patient, there are no guarantees that the patient will perform the test appropriately or even complete it at all.[11,12] As reported by Bamberger et al.,[7] given that a stone analysis is a more routinely performed test than a 24-hour urine study, we sought to identify any consistent urinary derangements associated with pure stone disease which could elucidate the etiology and perhaps even suggest the optimal management strategy for the prevention of recurrent nephrolithiasis in each subtype of SF.

Milose et al. demonstrated that only 7.4% of nearly 29,000 AUA guideline-defined "high-risk" SFs underwent a 24-hour urine study within six months of their stone event.[9,11] Furthermore, there are no comparative effectiveness trials demonstrating that therapy instituted on the basis of a 24-hour urine evaluation is superior to empiric therapy inherently driven by stone composition and clinical history.[10,12] Using stone composition to guide metabolic management has been described.[6,10] Empiric chlorthalidone and empiric potassium citrate have both been shown to effectively reduce stone events in recurrent CaOx SFs.[13,14] Our data provides additional support for the use of stone composition to guide prevention.

In cases of hypercalciuria, which has long been identified as the most common urinary derangement in calcium SFs,[15] we identified that pure AP, BRU, and COD SFs have

higher rates (calcium-to-creatinine ratio [Ca/Cr] > 140 mg/g, Table 3) and greater mean Ca/Cr (Table 2, Figure 1) compared to COM and UA SFs. Similar findings were published by Bamberger et al. and several previous studies with regards to COD (47-84%) versus COM (12-35%) SFs, while other studies have reported the same in BRU versus AP SFs.[7,16-19] As the cutoff defining hypercalciuria is quite arbitrary,[20] some have suggested lowering urinary calcium levels well below published cutoffs may be justified if stone activity continues.[21] Indeed, AUA guidelines recommend thiazides for recurrent calcium stones even in spite of a normal metabolic evaluation.[9] Likewise, while other clinical and metabolic factors must be considered, with such strong correlations to hypercalciuria in pure BRU and COD SFs, thiazides could be considered an appropriate empiric therapy for the prevention of stone recurrence.

Pure calcium SFs were also distinguished by oxalate excretion. We identified that pure COM SFs have greater mean oxalate excretion (Table 2, Figure 1) and the highest rate of hyperoxaluria (> 40 mg/d) compared to the other calcium stone subtypes (Table 3). As opposed to hypercalciuria, a difference in oxalate excretion based on crystalline phase of CaOx is less established, with some studies reporting differences and others not.[7,17,22] These discrepancies may be explained by how the authors defined a COM stone, with Bamberger et al. and our series using higher percent-compositions than Trinchieri et al. (60%) and Singh et al. (50%). The cutoff defining hyperoxaluria is also arbitrary and lower levels may lead to increased risk in idiopathic CaOx SFs.[20] Providers should target dietary changes to increase fluid, limit excessive oxalate intake, and complex available dietary oxalate with ingestible calcium for all CaOx SFs. Our results reinforce that pure COM SFs will likely benefit the most from these dietary changes based on their common urinary derangements.

Pure calcium stone subtypes were further distinguished by urinary pH, with AP and BRU SFs exhibiting higher mean pH (Table 2, Figure 1) and a greater prevalence of alkaluria (pH > 6.2) than the other groups (Table 3). It is well-established that alkaline urinary pH is a risk factor for CaP stones.[23] Pak et al. compared 24-hour urine parameters in patients with stones consisting of at least 70% AP, BRU, or CaOx, and demonstrated high urinary pH in CaP SFs but no difference between the BRU and AP subtypes.[19] The authors found a

difference in mean urinary pH in AP versus CaOx SFs, a finding that was corroborated by Singh et al. in a larger study.[22] Singh et al. also found a significant difference in mean urinary pH between those with majority-COD and majority-COM stones, similar to the findings of our series. Furthermore, we found a significantly higher rate of aciduria (pH < 5.8) in COM versus COD SFs (Table 3).

Urinary pH is often related to levels of urinary citrate, a known potent inhibitor of both CaOx and CaP stone formation. Hypocitraturia is another well-established urinary derangement associated with calcium stone disease, being present in 30-62% of calcium SFs.[15,24] In our series, urinary citrate excretion was quite variable; however, we found that mean citrate excretion was significantly lower in AP versus COD SFs (Table 2, Figure 1). In addition, AP SFs exhibited the highest rate of hypocitraturia (male: < 450 mg/d, female: < 550 mg/d) while COD SFs exhibited the lowest rate (Table 3). A difference in prevalence or degree of hypocitraturia amongst calcium stone subtypes is not well-established. Pak et al. did not find any significant differences in mean citrate excretion between AP, BRU, and CaOx SFs; but they did report low means in all of the groups.[19] Our findings reinforce that hypocitraturia is a frequent risk factor encountered in calcium stone disease, especially amongst CaP SFs. As with thiazide therapy, current AUA guidelines recommend potassium citrate for recurrent calcium SFs even in the absence of hypocitraturia.[9] Although controversial, alkali citrate is most suited for recurrent CaP SFs since their pH is already elevated and they are likely hypocitraturic.[23,25]

Pure UA SFs demonstrated lower mean urinary pH (Table 2, Figure 1) and a higher rate of aciduria (pH < 5.8) than the other groups (Table 3). UA SFs also had the highest mean supersaturation of UA despite exhibiting normal mean UA excretion (Table 2, Figure 1). We identified only 25.6% of pure UA SFs with hyperuricosuria ($\geq$ 0.8 g/d [male], $\geq$ 0.75 g/d [female]) and no significant differences in the prevalence of this derangement amongst the cohort (Table 3). As our study corroborates, uric acid stone disease is one of low urinary pH driving stone formation.[26] Previous studies have consistently demonstrated that pure or predominant UA SFs are older, have lower urinary pH, higher BMI, lower calcium excretion, and similar oxalate and uric acid excretion compared to pure or predominant CaOx SFs.[22,27] Studies analyzing urinary parameters in truly mixed CaOx/UA

SFs have demonstrated intermediate values relative to these "purer" forms.[26,28] Furthermore, both pure UA and mixed CaOx/UA stones are strongly associated with idiopathic low urine pH.[15,24] None of these studies have separated CaOx SFs by crystalline phase; however, we found that that idiopathic COM and UA stone disease may coexist on a spectrum defined by relatively similar urinary and clinical environments. In addition to urinary alkalization as mainstay medical therapy, depending on medical and dietary history, this spectrum of SFs should be especially targeted for counseling on lifestyle changes including physical activity and weight loss, strict glucose control, and DASH-style diets.[29]

This paper is not without limitations. This is a retrospective review of patients with nephrolithiasis over a long study period. It is possible that more patients had multiple stone events over time with different stone types, but data and commentary on prior and subsequent stone analyses are rather limited. We also acknowledge that our patients do not represent the vast majority of stone events, since most result as a mixture of different crystal structures at varying percent-compositions; and that further studies are needed to examine clinical and metabolic findings in patients with pure stones versus those with mixed stones. In addition, we cannot specify the proportion of pure stones in our population as we are unable to provide the number of mixed stones that were analyzed during the study period. However, we sought to find pure stones with an associated 24-hour urine evaluation to see if there were commonalities between the two available tests. To the best of our knowledge, no prior studies have compared urinary stone risk parameters in these five stone subtypes as defined by a 100% stone analysis and with as extensive of a clinical review. Importantly, our goal is not to supplant a 24-hour urine study with a stone analysis. We simply show that perhaps empiric interventions could be taken to prevent future stone events based on a stone analysis when a metabolic urine study is not available.

Conclusions:

Pure stone composition correlates with certain urinary and clinical characteristics as well as pathophysiologic trademarks. This study reinforces that not all pure stone subtypes are alike and unique metabolic derangements create specific urinary

environments. This data may be beneficial in guiding stone prevention in patients who cannot or are unwilling to perform a 24-hour urine study.

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Disclosures:

Dr. Amy Krambeck is a consultant for Boston Scientific Corporation and Lumenis. The other authors of this manuscript have no conflicts of interest to disclose as described by the *Journal of Endourology*.

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Abbreviations Used:

CaOx = calcium oxalate

COM = calcium oxalate monohydrate

COD = calcium oxalate dihydrate

CaP = calcium phosphate

AP = apatite

BRU = brushite

UA = uric acid

SFs = stone formers

Cr/Kg = creatinine-per-kilogram

Ca/Cr = calcium-to-creatinine ratio

Figure Legends:

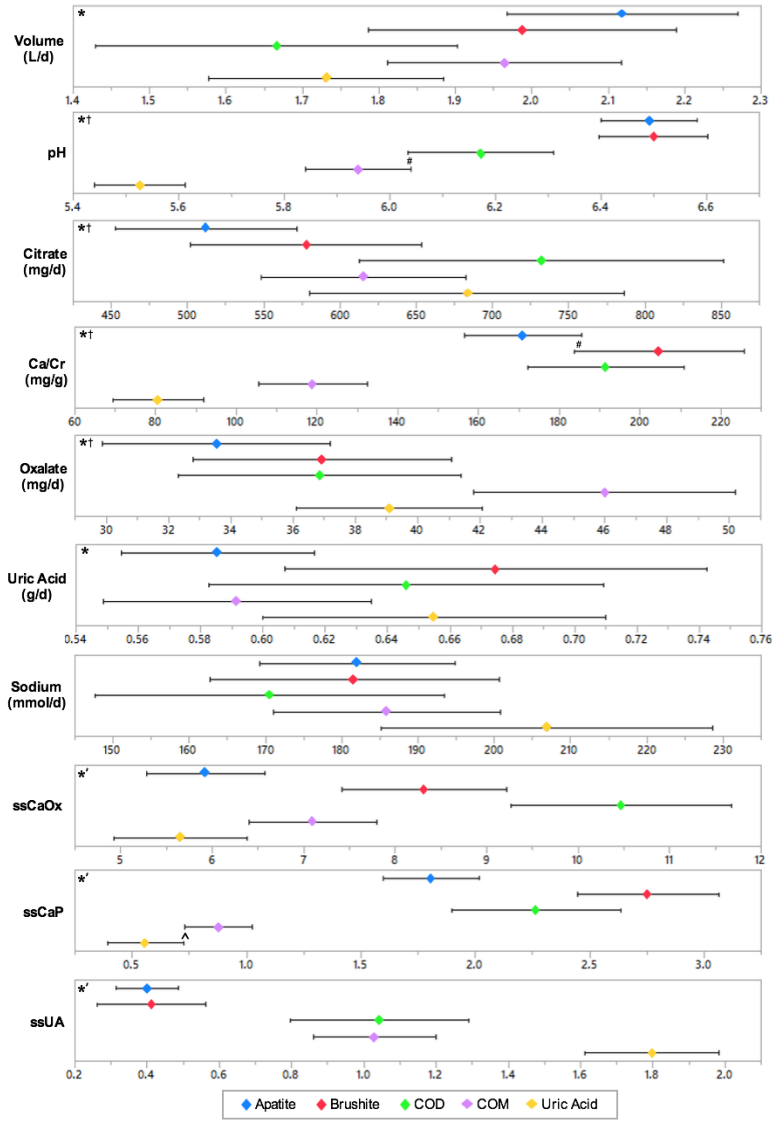

Figure 1. **Mean 24-hour urine stone risk factors with 95% confidence intervals**. Mean pairs with non-overlapping confidence intervals are significantly different as determined by post hoc Tukey-Kramer HSD testing unless marked with a ^ (n = 1). Conversely, pairs with overlapping confidence intervals are NOT statistically different unless marked with a # (n = 2).

*Denotes significance as determined by one-way ANOVA

†Denotes significance in nominal logistic fit model

'Not included in nominal logistic fit model

Table 1. Clinical characteristics of study patients

Parameter	Apatite	Brushite	COD	COM	Uric Acid	*p*-value
N, Total	121	54	50	104	82	
N, Male (%)	24 (**19.8**)	30 (55.6)	29 (58)	56 (53.8)	63 (**76.8**)	**< 0.0001***^{M} **< 0.0001***^{F}
Mean Age	44.7 ± 14.1	49.4 ± 15.8	42.2 ± 15.3	61 ± 12.8	57.5 ± 13.1	**0.0002***^{M} **< 0.0001***^{A}
Mean BMI	27.8 ± 6.3	28.8 ± 5.8	28.4 ± 6.73	31.5 ± 8.85	34.3 ± 7.6	ns^{M} **< 0.0001***^{A}
BMI > 30 (%)	33.6 ↓	39.6	36.1	46.8	69.4 ↑	**< 0.0001***^{F}
BMI > 25 (%)	62.8 ↓	77.1	75	81.9	91.7 ↑	**0.0001***^{F}
Median # of days b/w urine and stone (IQR)	21 (-32.5 – 54.5)	15 (-28.5 – 44.5)	36 (10.8 – 67)	-12 (-35 – 50.5)	37.5 (-4 – 76)	**0.0167***^{A}
Mean Ucr/Kg (mg/kg/d)	18.2 ± 4.56	19.5 ± 3.06	18.8 ± 4.9	17.3 ± 5.29	18.9 ± 3.04	0.3175^{A}
Crohn,	1.67	0	0	19.2 ↑	2.6	**<**

bariatric, or SBS (%)						**0.0001*[F]**
End ileostomy (%)	0	0	0	0	8.54 ↑	**< 0.0001*[F]**
HyperPTH (%)	6.67	17 ↑	4.17	2.91	0 ↓	**0.0008*[F]**
HTN (%)	27.5 ↓	40.8	0.9 ↓	62.1 ↑	77.3 ↑	**< 0.0001*[F]**
DM (%)	7.5 ↓	6.12 ↓	20.9	26.2	45.3 ↑	**< 0.0001*[F]**
DLD (%)	12.5 ↓	30.6	31	50.5 ↑	52 ↑	**< 0.0001*[F]**
ASCVD (%)	4.17 ↓	14.3	4.76	27.2 ↑	17.3	**< 0.0001*[F]**
Gout (%)	1.69 ↓	2	4.88	12.8 ↑	10.7	**0.0039*[F]**

*Denotes significance

[A]ANOVA

[F]Fisher's exact test

[M]Multivariate model (included variables also underlined)

↑Denotes proportion is significantly higher on analysis of means for proportions

↓Denotes proportion is significantly lower on analysis of means for proportions

IQR = interquartile range; SBS = short bowel syndrome; HTN = hypertension; DM = diabetes mellitus; DLD = dyslipidemia; ASCVD = clinical atherosclerotic cardiovascular

disease (history of coronary artery disease [+/- acute coronary syndrome], stroke or transient ischemic attack, or peripheral vascular disease)

Table 2. Mean ± SD for each 24-hour urine stone risk or dietary factor

	Parameter	Apatite	Brushite	COD	COM	Uric Acid	*p*-value
Independent Parameters	Volume (L/d)	2.12 ± 0.84	1.99 ± 0.74	1.67 ± 0.83	1.96 ± 0.79	1.73 ± 0.70	ns[M] **0.0012***[A]
	Calcium (mg/d)	242.2 ± 119.7	320.6 ± 115.2	297.1 ± 136.3	187.8 ± 108.8	159.4 ± 117.4	**< 0.0001***[M]
	(mmol/d)	6.04 ± 2.99	8 ± 2.87	7.41 ± 3.4	4.69 ± 2.71	3.98 ± 2.93	**< 0.0001***[A]
	Oxalate (mg/d)	33.5 ± 20.3	36.9 ± 15.2	36.8 ± 16	46 ± 21.5	39.1 ± 13.5	**< 0.0001***[M]
	(mmol/d)	0.38 ± 0.23	0.42 ± 0.17	0.42 ± 0.17	0.52 ± 0.24	0.44 ± 0.15	**< 0.0001***[A]
	Citrate (mg/d)	512.1 ± 331.1	577.8 ± 277.5	732.2 ± 420.2	615.2 ± 344.5	683.2 ± 470	**0.0062***[M] **0.0018***[A]
	(mmol/d)	2.71 ± 1.75	3.06 ± 1.47	3.87 ± 2.22	3.25 ± 1.82	3.61 ± 2.49	
	pH	6.49 ± 0.5	6.5 ± 0.38	6.17 ± 0.49	5.94 ± 0.51	5.53 ± 0.39	**< 0.0001***[M] **< 0.0001***[A]
	Uric Acid (g/d)	0.59 ± 0.17	0.67 ± 0.25	0.65 ± 0.22	0.59 ± 0.22	0.65 ± 0.25	ns[M] **0.0288***[A]
	(mmol/d)	3.48 ± 1.03	4.01 ± 1.47	3.84 ± 1.33	3.52 ± 1.31	3.9 ± 1.49	

	Sodium (mmol/d)	182 ± 71.4	181.7 ± 69.4	170.6 ± 80.7	185.9 ± 76.6	206.9 ± 98.9	ns[M] 0.0955[A]
	Potassium (mmol/d)	61.7 ± 29.2	58.8 ± 25.9	55.6 ± 24.1	59.5 ± 25.1	69.9 ± 27.2	**0.0017*[M]** **0.0208*[A]**
	Magnesium (mg/d)	105.3 ± 50	118.2 ± 38.7	109.7 ± 40.1	102.2 ± 41.5	104.5 ± 52.5	ns[M] 0.2976[A]
	Phosphorus (g/d) (mmol/d)	0.87 ± 0.32 28.2 ± 10.5	0.99 ± 0.3 32.1 ± 9.53	0.92 ± 0.35 29.8 ± 11.3	0.93 ± 0.34 30.1 ± 10.8	1.15 ± 0.39 37.2 ± 12.6	ns[M] **< 0.0001*[A]**
	Ammonium (mmol/d)	32 ± 15.3	32.6 ± 12.7	33 ± 17.1	30 ± 12.4	33.7 ± 16.5	ns[M] 0.5095[A]
	Chloride (mmol/d)	173 ± 68.3	170.3 ± 61.4	157.3 ± 72.7	179.3 ± 74.1	200.1 ± 90.1	ns[M] **0.0161*[A]**
	Sulfate (mmol/d)	35.9 ± 14.3	37.1 ± 13.8	37.5 ± 15.2	35.2 ± 16	49.4 ± 19.8	ns[M] **< 0.0001*[A]**
	Urea Nitrogen (g/d)	9.86 ± 3.26	9.89 ± 3.78	9.58 ± 3.6	10.4 ± 3.96	13 ± 5.02	**0.0010*[M]** **< 0.0001*[A]**
Derived Parameters	Ca/Kg (mg/kg/d)	3.14 ± 1.56	3.99 ± 1.44	3.53 ± 1.15	2.08 ± 1.23	1.5 ± 0.93	**< 0.0001*[A]**
	Ca/Cr (mg/d / g/d)	171 ± 80.3	204.7 ± 77.4	191.5 ± 68.4	118.9 ± 69.6	80.7 ± 51.1	**< 0.0001*[A]**

	(mmol/d / mmol/d)	0.48 ± 0.23	0.58 ± 0.22	0.54 ± 0.2	0.34 ± 0.2	0.23 ± 0.14	
	SS CaOx	5.93 ± 3.6	8.32 ± 3.31	10.5 ± 4.26	7.1 ± 3.59	5.65 ± 3.31	**< 0.0001*** [A]
	SS CaP	1.81 ± 1.16	2.76 ± 1.13	2.27 ± 1.3	0.88 ± 0.75	0.56 ± 0.76	**< 0.0001*** [A]
	SS UA	0.4 ± 0.48	0.41 ± 0.55	1.04 ± 0.87	1.03 ± 0.87	1.8 ± 0.84	**< 0.0001*** [A]

*Denotes significance

[A]ANOVA

[M]Multivariate model (included variables also underlined)

SS = relative supersaturation rate

Table 3. Metabolic findings of study patients

	Apatite	Brushite	COD	COM	Uric Acid	*p*-value[F]
Hypercalciuria (%)	66.1 ↑	79.6 ↑	82 ↑	24 ↓	14.6 ↓	**< 0.0001***
Hyperoxaluria (%)	19 ↓	40.7	30	51.9 ↑	34.2	**< 0.0001***
Hypocitraturia (%)	55.4 ↑	38.9	30	37.5	41.5	**0.0132***
Aciduria (%)	9.09 ↓	3.7 ↓	24	47.1 ↑	82.9 ↑	**< 0.0001***
Alkaluria (%)	72.7 ↑	79.6 ↑	46	31.7 ↓	6.1 ↓	**< 0.0001***
Hyperuricosuria (%)	19	27.8	28	18.3	25.6	0.3734
Hypernatriuria (%)	65.3	66.7	52	67.3	73.2	0.1831
Hypomagnesuria (%)	15.7	5.6	6	11.5	19.5	0.0658

[F]Fisher's exact test

↑Denotes proportion is significantly higher on analysis of means for proportions

↓Denotes proportion is significantly lower on analysis of means for proportions