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Calcium stone disease: a multiform reality

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Abstract In calcium renal stones, calcium oxalate and calcium phosphate in various crystal forms and states of hydration can be identified. Calcium oxalate monohydrate (COM) or whewellite and calcium oxalate dihydrate (COD) or weddellite are the commonest constituents of calcium stones. Calcium oxalate stones may be pure or mixed, usually with calcium phosphate or sometimes with uric acid or ammonium urate. The aim of this study was to compare the clinical and urinary patterns of patients forming calcium stones of different composition according to infrared spectroscopic analysis in order to obtain an insight into their etiology. The stones of 84 consecutive calcium renal stone formers were examined by infrared spectroscopy. In each patient, a blood sample was drawn and analysed for serum biochemistry and a 24-h urine sample was collected and analysed for calcium, phosphate, oxalate, citrate and other electrolytes. We classified 49 patients as calcium oxalate monohydrate (COM) stone formers, 32 as calcium oxalate dihydrate (COD) stone formers and three as apatite stone formers according to the main component of their stones. Patients with COM stones were significantly older than patients with COD stones ($P < 0.002$). Mean daily urinary calcium and urinary saturation with respect to calcium oxalate were significantly lower in patients with COM than in those with COD stones ($P < 0.000$). Patients with calcium oxalate stones containing a urate component ($\leq 10\%$) presented with higher saturation ($P < 0.012$) with respect to uric acid in their urine (and lower with respect to calcium oxalate and calcium phosphate, respectively $P < 0.024$ and $P < 0.003$) in comparison with patients without a urate component in the stone. Patients with calcium oxalate stones with a calcium phosphate component ($\geq 15\%$) showed higher ($P < 0.0016$) urinary saturation levels with respect to calcium phosphate (and lower with respect to uric acid ($P < 0.009$), compared with patients forming stones without calcium phosphate or with a low calcium phosphate component. Patients with calcium stones mixed with urate had a significantly lower urinary pH ($P < 0.002$) and urinary calcium ($P < 0.000$), and patients with calcium phosphate $> 15\%$, higher urinary pH ($P < 0.004$) and urinary calcium ($P < 0.000$). In conclusion, in the evaluation of the individual stone patient, an accurate analysis of the stone showing its exact composition and the eventual presence of minor components of the stone is mandatory in order to plan the correct prophylactic treatment. Patients with "calcium stones" could require various approaches dependent on the form and hydration of the calcium crystals in their stones, and on the presence of "minor" crystalline components that could have acted as epitaxial factors.

Keywords Renal calcium oxalate stone · Urinary calcium · Calcium oxalate monohydrate · Calcium oxalate dihydrate · Apatite · Uric acid

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Introduction

Kidney stones are classified on the basis of their crystalline component, calcium crystals being the more frequent.

The more common forms of calcium crystals that precipitate in the urine are calcium oxalate as monohydrate (COM) or whewellite, calcium oxalate dihydrate (COD) or weddellite, and calcium phosphate as hydroxyapatite, brushite and octacalcium phosphate.

Calcium stones may be apparently pure or mixed when calcium oxalate is mixed with calcium phosphate and sometimes with uric acid or ammonium urate.

It is commonly accepted that calcium containing stones are a unitary disease whatever their exact composition. Overexcretion of calcium and oxalate together with reduced urinary volume and lack of crystallization inhibitors in the urine are recognized as common main causes of calcium stone disease, and different types of calcium stones are treated as a unit.

In our opinion, different causes of the crystallization of different types of calcium stones may be recognized, allowing for selective treatment modalities.

Therapy for stone disease should be based on the analysis of calculi, although the most common type of analysis of urinary calculi is still chemical, which is not suitable for the accurate identification of minor components.

On the other hand, knowledge of the percentage composition of a urinary calculus contributes to the ability to predict the most probable cause of that calculus. Therefore, it is critical that the laboratory be capable of providing accurate quantitative analysis of the calculus by suitable methods, such as x-ray diffraction or infrared spectroscopy, which allow the detection of minor components in mixed urinary calculi.

The aim of this study was to compare the clinical and urinary patterns of patients forming calcium stones of different compositions according to infrared spectroscopic analysis in order to obtain an insight into their etiology.

Materials and methods

The stones of 84 consecutive calcium renal stone formers were examined by infrared spectroscopy in our outpatient stone clinic. The stones were classified according to their main component as COM, COD or apatite if, respectively, the content of COM, COD or apatite was $>60\%$ of the total composition of the stone.

Patients with known causes of calcium stone formation, such as primary hyperparathyroidism, overt distal renal tubular acidosis, medullary sponge kidney, sarcoidosis, or other less frequent hypercalciuric conditions, were excluded.

All patients were routinely asked about their family history of stones, past medical history related to stone disease (steroid therapy, hyperthyroidism, chronic diarrhea, prolonged immobilization), working activity and standard of living. Height and weight were recorded at the time of the investigation.

A fasting blood sample was drawn in order to measure creatinine, sodium, potassium, calcium, magnesium, phosphorus and uric acid. A 24-h urine collection, while on a random diet, was performed for each patient. Urine volume and the concentration of creatinine, sodium, potassium, calcium, magnesium, phosphate, urate, oxalate and citrate were measured.

Sodium and potassium were determined by flame photometry; calcium, magnesium, phosphate, urate and creatinine with routine spectrophotometric methods. Oxalate was measured using oxalate oxidase and citrate using citrate lyase. Urine samples were analyzed for pH by a Corning pH meter. The state of urinary saturation with respect to calcium oxalate, calcium phosphate and uric acid was estimated by means of a computer-based model (URSUS), whereby a value of 1 denotes saturation, and >1 supersaturation [1].

Results are presented as means $\pm$ SD. Statistical analyses were performed using the SPSS 11.5 package. Group differences were compared by unpaired *t*-test or one-way ANOVA with post hoc multiple comparisons according to Bonferroni. These comparisons were considered significantly different if $P<0.05$.

Results

In the great majority of cases, stones were mixed; we observed only two stones of pure whewellite.

We classified 49 patients (58%) as COM stone formers (mean age at stone onset 41.8 ± 18.4 years, weight 66 ± 15 kg, height 166 ± 11 cm, male:female ratio 34:15), 32 as COD stone formers (mean age at stone onset 30.3 ± 10.3 years, weight 71 ± 11 kg, height 172 ± 7 cm, male:female ratio 25:7) and three as apatite stone formers (mean age at stone onset 19.3 ± 5.0 years, weight 64 ± 16 kg, height 171 ± 8 cm, male:female ratio 2:1).

Patients with COM stones were significantly older at the onset of stone disease than patients with COD stones ($P<0.002$). Weight and height were not significantly different between the three groups.

The means $\pm$ SD of the more relevant biochemical parameters for the patients with COM, COD and apatite stones are shown in Tables 1 and 2.

Table 1 Serum chemistry in patients with different types of stone (COM calcium oxalate monohydrate, COD calcium oxalate dihydrate, CAP apatite)

	COM	COD	CAP	*P*
K (mEq/l)	4.13 ± 0.27	4.18 ± 0.33	4.16 ± 0.20	0.95
Na (mEq/l)	141 ± 1.7	140 ± 1.4	140 ± 1.5	0.81
Ca (mg/dl)	9.32 ± 0.43	9.36 ± 0.33	9.66 ± 0.06	0.31
Mg (mg/dl)	2.18 ± 0.30	2.20 ± 0.31	2.07 ± 0.24	0.65
P (mg/dl)	3.33 ± 0.56	3.27 ± 0.69	3.08 ± 0.49	0.78
UA (mg/dl)	4.86 ± 1.41	5.11 ± 1.22	4.63 ± 1.20	0.76
Cr (mg/dl)	1.00 ± 0.16	1.01 ± 0.15	1.01 ± 0.25	0.88

Table 2 The 24 h urine in patients with different types of stone

	COM	COD	CAP	*P*
pH	5.56 ± 0.53	5.63 ± 0.43	5.93 ± 0.11	0.41
Volume (ml/day)	1,748 ± 690	1,898 ± 966	1,233 ± 160	0.24
Potassium (mEq/day)	62 ± 21	63 ± 18	51 ± 12	0.51
Sodium (mEq/day)	181 ± 74	163 ± 51	167 ± 47	0.73
Calcium (mg/day)	210 ± 106	334 ± 134	347 ± 157	0.000
Magnesium (mg/day)	93 ± 32	97 ± 30	64 ± 44	0.27
Urate (mg/day)	571 ± 195	655 ± 196	525 ± 235	0.49
Citrate (mg/day)	507 ± 264	487 ± 247	339 ± 233	0.43
Oxalate (mg/day)	26.3 ± 12.2	26.7 ± 12.1	13.0 ± 8.8	0.88
Phosphate (mg/day)	734 ± 265	823 ± 273	668 ± 177	0.28
CaOx saturation	4.85 ± 3.10	7.35 ± 3.61	3.27 ± 0.52	0.002
$CaPO_4$ saturation	1.07 ± 1.61	1.83 ± 2.23	3.05 ± 3.29	0.082
UA saturation	1.41 ± 1.16	1.33 ± 1.03	0.68 ± 0.26	0.52

Mean urinary saturation with respect to calcium oxalate was significantly higher in COD stone formers than in COM stone formers ($P < 0.002$), and mean daily urinary calcium was significantly lower in patients with COM than in those with COD stones ($P < 0.000$).

On the contrary, the mean values of all of the other measured biochemical parameters were not significantly different between the groups.

Only 16% (8/49) of the COM stone formers were hypercalciuric in comparison with 50% (16/32) of the COD stone formers.

In order to obviate to possible bias related to sex, the means ± SD of the more relevant biochemical parameters for the patients with COM and COD stones divided by sex, were calculated and reported in Table 3. In fact, the mean daily urinary excretion of calcium among patients with COM stones was significantly lower ($P < 0.000$) than among patients with COD stones in both male and female patients.

Table 3 The 24 h urine in patients with COM and COD by gender

	COM	COD	*P*
Males			
n	34	25	
pH	5.54 ± 0.53	5.65 ± 0.45	0.42
Volume (ml/day)	1,665 ± 679	1,885 ± 997	0.43
Potassium (mEq/day)	67 ± 21	65 ± 18	0.67
Sodium (mEq/day)	200 ± 76	164 ± 54	0.41
Calcium (mg/day)	211 ± 101	335 ± 135	0.000
Magnesium (mg/day)	98 ± 33	97 ± 32	0.95
Urate (mg/day)	606 ± 180	681 ± 204	0.13
Citrate (mg/day)	525 ± 288	445 ± 243	0.25
Oxalate (mg/day)	25.7 ± 13.1	27.3 ± 12.7	0.62
Females			
n	15	7	
pH	5.60 ± 0.54	5.55 ± 0.31	0.84
Volume (ml/day)	1,915 ± 703	2,150 ± 854	0.49
Potassium (mEq/day)	51 ± 15	55 ± 12	0.64
Sodium (mEq/day)	142 ± 53	161 ± 41	0.40
Calcium (mg/day)	210 ± 119	333 ± 138	0.000
Magnesium (mg/day)	84 ± 30	94 ± 20	0.41
Urate (mg/day)	500 ± 209	549 ± 124	0.58
Citrate (mg/day)	472 + -214	656 ± 194	0.066
Oxalate (mg/day)	27.5 ± 10.5	24.0 ± 9.9	0.47

When the minor components of stones were considered, we observed 26 patients with calcium oxalate stones mixed with uric acid/ammonium urate (equal or less than 10%) (CAOX/UA) and 15 patients with calcium oxalate stones mixed with a > 15% component of apatite (CAOX/CAP).

Urinary saturation for uric acid was significantly ($P < 0.012$) higher in patients with mixed CAOX/UA stones than in patients with calcium oxalate stones (CAOX) without a minor uric acid/urate component, while saturation with respect to calcium oxalate and calcium phosphate was significantly higher (respectively, $P < 0.024$ and $P < 0.003$)(Table 4).

The higher saturation for uric acid in patients with mixed CAOX/UA stones was related to lower values of urinary pH. No difference for urinary oxalate, citrate, phosphate and urinary volume were observed, whereas urinary calcium was significantly lower in patients with mixed CAOX/UA stones compared to patients with calcium oxalate stones (CAOX) without a minor uric acid/urate component.

Urinary saturation for calcium phosphate was significantly higher ($P < 0.0016$), and urinary saturation for uric acid significantly lower ($P < 0.009$) in 15 patients with mixed CAOX/CAP stones (with > 15% of apatite) than in 69 patients with calcium oxalate stones without a calcium phosphate component or with a lower (< 5%) apatite component (Table 5).

Table 4 The 24 h urine in patients with calcium oxalate stones mixed or not with a minor amount (equal or less than 10%) of uric acid/ammonium urate (CAOX-UA vs CAOX)

	CAOX	CAOX/UA	*P*
N°pts	55	26	
pH	5.70 ± 0.45	5.35 ± 0.50	0.002
Volume (ml/day)	1,880 ± 909	1,711 ± 590	0.38
Calcium (mg/day)	288 ± 121	194 ± 124	0.0002
Urate (mg/day)	604 ± 178	604 ± 244	1.00
Citrate (mg/day)	497 ± 218	527 ± 319	0.51
Oxalate (mg/day)	26.2 ± 11.6	27.7 ± 13.1	0.60
CaOx saturation	6.44 ± 3.75	4.57 ± 2.55	0.024
$CaHPO_4$ saturation	1.80 ± 2.16	0.46 ± 0.45	0.003
UA saturation	1.17 ± 0.93	1.83 ± 1.31	0.012

Table 5 The 24 h urine in patients with calcium stones containing or not calcium phosphate (CAP > 60%, CAP < 10%, CAP−)

	CAP−	CAP < 5%	CAP > 15%	*P*
n	45	24	15	
pH	5.63 ± 0.46	5.36 ± 0.51	5.86 ± 0.34	0.005
Volume (ml/day)	1,703 ± 790	1,720 ± 605	1,805 ± 813	0.66
Calcium (mg/day)	275 ± 117	185 ± 110	342 ± 141	0.000
Urate (mg/day)	583 ± 177	618 ± 248	627 ± 191	0.68
Citrate (mg/day)	503 ± 223	515 ± 294	472 ± 283	0.87
Oxalate (mg/day)	24.8 ± 11.5	28.2 ± 13.6	27.4 ± 12.0	0.49
CaOx saturation	6.26 ± 3.69	4.56 ± 2.66	6.84 ± 3.86	0.09
$CaHPO_4$ saturation	1.68 ± 2.05	0.47 ± 0.47	2.03 ± 2.52	0.016
UA saturation	1.30 ± 0.96	1.86 ± 1.35	0.71 ± 0.58	0.009

The higher saturation of calcium phosphate in patients with calcium phosphate > 15% was related to higher values of urinary calcium ($P < 0.000$) and urinary pH ($P < 0.004$), whereas no differences for urinary oxalate, citrate, phosphate or urinary volume were observed (Table 5).

Discussion

In economically developed countries, calcium stones account for 70–80% of all kidney stones [2, 3].

In calcium stones, calcium oxalate and calcium phosphate, each in various crystal forms and states of hydration, could be identified. Recently, an increase in urinary tract stone prevalence has been reported [4], mainly related to an increase in calcium oxalate stones. An increase in the proportion of COM with respect to the proportion of COD stones has been recorded [5, 6]. The reason for the increase of COM and the decrease of COD stones is unclear. This observation could be explained by changes in environmental and dietary factors or by the influence of new less invasive procedures for stone removal, but a definite explanation requires additional data. In fact, at present no differences in the crystallization process of these two types of oxalate are known.

In the 1960s, Murphy and Pyrah [7] studied the composition and the detailed structure of calcium oxalate renal calculi by x-ray diffraction, polarising microscopy, and microradiography, suggesting that there are two main types of calcium oxalate calculi. In one, named the "crystalline" type due to the well formed crystalline material, both COM and COD occurred together with apatite; in the other, named the "striated" type due to the dendritic aspect of the crystalline component, COM was always found with apatite in separate layers. It was suggested that they are formed either by the crystallization of COD from urine with secondary recrystallization of COD into COM, in the case of "crystalline" calculi, or by the association with their organic component, in the case of "striated" calculi. A higher calcium excretion in the patients forming COD "crystalline" stones was found than in those forming COM "striated" stones, confirming the hypothesis that COD stones are formed primarily by crystallization from the urine. The authors assumed that the growth of COM is inhibited by some component of normal urine and that COM stones could occur primarily by the coacervation of organic colloids at normal electrolyte concentrations. After 40 years, this pioneering study is still actual in some aspects, although the "colloid" theory of stone formation is debatable.

More recently, Finlayson's group [8] wrote that the "formal rules for weddellite (COD) production have not been enunciated". Their experimental observations showed that COD is favored by a high free calcium to free oxalate ratio and a low initial relative supersaturation. The reason for the first condition is not known, while the second condition is probably explained by the high apparent activation energy at low relative supersaturation for the COD nucleation rate compared to COM. Furthermore, they were not able to produce pure COD without large amounts of citrate and magnesium: the resulting pure COD was unstable and underwent solution mediated transformation to COM.

Daudon and coworkers [9, 10] demonstrated that COM stones are mainly associated with hyperoxaluria, and those composed of COD with hypercalciuria. In first-morning voided urine, they observed that the incidence of calcium oxalate crystals appeared to depend on the molar product, whereas the type of crystals (mono or dihydrate) depended on the calcium to oxalate ratio. Only COM crystals were observed in fresh urine specimens whose calcium to oxalate ratio was < 6, and COD crystals in specimens with a ratio > 14.

We confirmed the striking association between hypercalciuria and COD stones, but we were not able to show a higher urinary oxalate excretion in patients with COM stones compared to those with COD stones. On the other hand, in most of the patients with COM stones we were not able to show any alteration in the urinary risk factors for calcium stones.

COM formation could result from episodic or transient increases of oxalate excretion or from other "unknown" etiological factors, but these hypotheses need further evidence.

On the other hand, COM stones seem to be the consequence of a weaker stone "activity" because they tend to occur at an older age with respect to COD

stones. Finally, COD stones could be stones in which the transformation from COD to COM is incomplete because of a recent or ''fast'' formation.

The understanding of the complex mechanisms of calcium stone formation is made even more difficult when taking into account the presence of minor components of the stone.

A lot of evidence has been accumulated suggesting that an excess of urinary urate is associated with the formation of calcium oxalate stones [11, 12], and it is well known that calcium oxalate and uric acid have crystal lattices similar enough to permit the deposit of one type of crystal upon the surface of another due to the process called epitaxy. It has also been suggested that the normal inhibition of crystal growth by urine is disturbed by the presence of urate and that urate also combines with uromucoid enhancing the production of an insoluble matrix from its soluble precursor in urine.

Finally, Coe and Kavalach [13] reported a reduction in stone formation with allopurinol therapy in recurrent calcium oxalate stone formers who had hyperuricosuria as a sole detectable abnormality.

It has also been observed that the degree of alkalinity of urine is the major determinant of the amount of calcium phosphate present in the stone [14]; calcium phosphate being considered as secondarily added to calcium oxalate stones. Only in the renal tubular acidosis (RTA) patients did pH appeared to play a prime role in the genesis of the stones consisting essentially of ''pure'' calcium phosphate.

In conclusion, we have demonstrated that patients forming COM and COD stones show different clinical and biochemical patterns. This observation implies different mechanisms for the process of stabilization of different calcium oxalate hydrates. We also confirmed the biochemical heterogeneity of urine from patients with calcium oxalate stones containing ''minor'' components other than calcium oxalate.

In clinical practice these observations are not often taken into consideration. On the contrary, we would like to stress that in the evaluation of the individual stone patient, an accurate analysis of the stone showing its exact composition and the presence of minor crystal components is mandatory in order to plan the correct prophylactic treatment.

Patients with ''calcium stones'' could deserve a different approach in relation to the form and hydration of the calcium crystals, and to the presence of ''minor'' crystalline components that could act as epitaxial factors.

Manipulation of urinary pH or administration of drugs active on uric acid metabolism could be suitable in selected patients, in addition to or as an alternative to measures aimed to control calcium and/or oxalate excretion.

However, further studies are still warranted in order to obtain a more complete knowledge on the pathogenic mechanisms of calcium oxalate stone formation to better explain the changing epidemiology of calcium stones.

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