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Calcium phosphate: an important crystal phase in patients with recurrent calcium stone formation?

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Summary. Stone and urine composition were analysed in 75 men and 40 women with recurrent calcium oxalate stone disease (group R) and in 48 men and 19 women who had formed only one calcium-oxalate-containing stone (group S). Patients who had developed stones with a large fraction of calcium phosphate were significantly more frequent in group R than in group S. There was furthermore a higher excretion of calcium and higher calcium oxalate supersaturation levels in patients with stones containing more than 25% calcium phosphate. It was concluded from these observations that the calcium phosphate content of renal stones might be a useful factor in predicting the future course of the disease.

Key words: Calcium oxalate – Calcium phosphate – Recurrent stone formation – Renal stones – Urine composition

It is well recognized that patients with calcium stone disease suffer a high risk of forming new stones after their first stone episode. The recurrence rate varies between different studies, certainly as a result of how patients have been selected, and values up to 60–70% during a 10-year period have been reported [2, 7, 28, 35]. A careful follow-up of stone formers is therefore indicated, in order to obtain information on the course of the disease in the individual patient. Knowledge of the activity of the stone disease and the identification of possible risk factors provides a basis for appropriate advice and treatment, with the aim of preventing the formation of new stones. Such an investigation doubtless requires considerable organization and very good patient compliance. It also implies a significant economic burden on both the patient and the health care system. Although effective medical treatment with an adequate follow-up programme is very important for patients suffering from frequent stone recurrences and stone growth, such measures become less important for patients with infrequent stone formation and are obviously without meaning in those who will form only a single stone during their life. As many as 30–40% of stone formers might belong to this latter category. It would therefore be highly desirable to have methods that allow the prediction of the future course of the disease and thereby enable identification of those patients most likely to benefit from a prophylactic programme.

In a previous study we observed that recurrent stone formation after extracorporeal shock wave lithotripsy was more frequent in patients who had formed stones with a high content of calcium phosphate [34]. To determine whether analysis of stone composition might be of value for discriminating between recurrent and single stone formers we compared urine and stone composition in a group of calcium oxalate stone formers treated with extracorporeal shock wave lithotripsy.

Materials and methods

The subjects included in this retrospective study of urine and stone composition comprised a consecutive group of patients treated with extracorporeal shock wave lithotripsy for non-infected idiopathic calcium oxalate stones. We only considered stones containing some fraction of calcium oxalate.

There were 67 patients who were treated for their first and only stone (group S), comprising 48 men (mean age 57 years) and 19 women (mean age 57 years). The finding of more than one stone on treatment or a history of previous stone formation were recorded in 108 patients (group R), of whom 75 were men (mean age 58 years) and 40 were women (mean age 59 years). The decision as to whether the patient belonged to group R or group S was made at the time of shock wave lithotripsy, and any subsequent information on recurrent stone formation after this treatment was not taken into account.

Stone material was analysed with a wet chemical procedure [17] and the approximate content of different stone salts estimated by means of an algorithm. On the basis of their content of calcium oxalate and calcium phosphate the stones were classified as follows: CaOx, stones composed of pure calcium oxalate; CaOx(CaP), stones composed of calcium oxalate with up to 25% (w/w) calcium phosphate; CaOxCaP, stones composed of calcium oxalate with more than 25% calcium phosphate; and CaP(CaOx), stones composed of calcium phosphate with less than 25% calcium oxalate.

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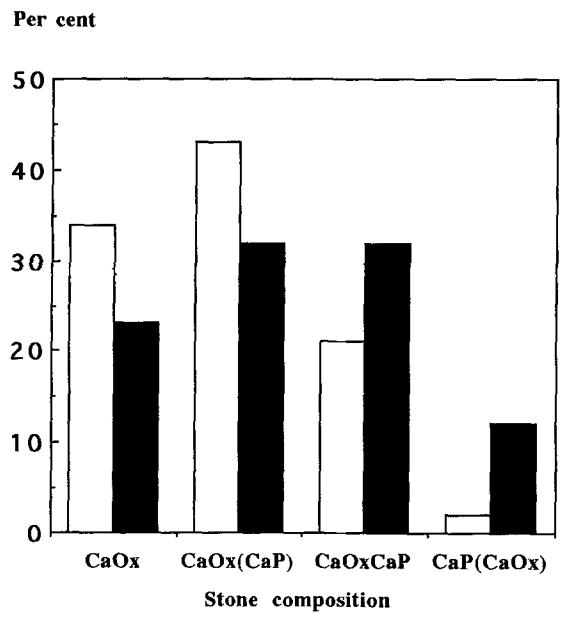

Fig. 1. The relative frequency of calcium oxalate (CaOx)-containing stones with a different content of calcium phosphate (CaP) in patients who had formed only one stone (group S, *open columns*) and in patients with recurrent stone formation (group R, *filled columns*). For explanation of stone composition see text

Table 1. Distribution of men and women in groups S and R in relation to stone composition

Stone composition	Group S		Group R	
	Men	Women	Men	Women
CaOx	17 (35%)	6 (32%)	19 (25%)	8 (20%)
CaOx(CaP)	22 (46%)	7 (37%)	29 (39%)	8 (20%)
CaOxCaP	9 (19%)	5 (26%)	21 (28%)	16 (40%)
CaP(CaOx)	0 (0%)	1 (5%)	6 (8%)	8 (10%)

For definitions of stone composition see text

Table 2. Ratio between the number of patients in group R and the number of patients in group S for different compositions of stones

Stone compostion	Men	Women	Men + women
CaOx	1.12	1.33	1.17
CaOx(CaP)	1.32	1.14	1.28
CaOxCaP	2.33	3.20	2.64
CaP(CaOx)	>6	8.0	14.0

Table 3. Male/female ratio in the different subgroups

Stone composition	Group S	Group R	All patients
CaOx	2.8	2.4	2.6
CaOx(CaP)	3.1	3.6	3.4
CaOxCaP	1.8	1.3	1.4
CaP(CaOx)	0	0.75	0.75

Urine composition was analysed in 24-h samples collected in bottles containing 15 ml of 6 mol/l hydrochloric acid. All urine collections were carried out before the lithotripsy procedure. The excretion of calcium, oxalate, citrate and magnesium were determined with methods previously described in detail [6]. At the time when these urine samples were analysed, phosphate was not included in our routine analytical programme; neither was it possible to measure pH because of the acid preservative.

Estimates of the risk of forming urine supersaturated with respect to calcium oxalate were expressed in terms of an AP(CaOx) index [30]:

$$1.9 \times Ca^{0.85} \times Ox \times Cit^{-0.22} \times Mg^{-0.12} \times V^{-1.03}$$

and an AP(CaOx) index (s), the latter calculated for a standardized 24-h urine volume of 1500 ml [32]:

$$2.9 \times Ca^{0.85} \times Ox \times Cit^{-0.22} \times Mg^{-0.12}$$

In both indices the factors and exponents were adjusted to get the best approximation to ion activities calculated with the EQUIL 2 programme [33]. The excretion of calcium (Ca), oxalate (Ox), citrate (Cit) and magnesium (Mg) was expressed in millimoles per 24 h and urine volume (V) in litres. The normal 24-h excretion limits for calcium were 7.5 mmol in men and 6.5 mmol in women, and for oxalate were 0.45 and 0.44 mmol for men and women respectively. The lower limits for excretion in men and women were 3.0 and 2.5 mmol for magnesium and 1.5 and 1.4 mmol for citrate. The upper normal limits for both AP(CaOx) index and AP(CaOx) index (s) were set to 2.3 for men and 2.0 for women.

Statistical analysis was carried out by comparing mean urine variables using Student's t-test and frequencies using chi-square analysis.

Results

The composition of stones in patients from groups S and R is shown in Fig. 1 and summarized for men and women in Table 1. Whereas calcium-oxalate-dominated stones were most common among patients in the former group, stones with a high content of calcium phosphate were apparently more frequently associated with recurrent stone disease. Although there was no significant difference in terms of previous stone formation between patients who had formed CaOx stones and those who had formed CaOx(CaP) stones ($P > 0.25$), the number of patients belonging to group R was significantly greater in the group who had formed either CaOxCaP or CaP (CaOx) stones ($P < 0.025$; chi-square = 5.76) than in the group with pure CaOx stones. The fraction of recurrent stone formers was also significantly larger among the patients with CaOxCaP and CaP(CaOx) stones than among those with CaOx and CaOx(CaP) stones ($P < 0.005$; chi-square = 7.91). There was, however, no significant difference when all patients who had formed calcium-phosphate-containing stones were compared with those who had pure calcium oxalate stones. The difference in relation to the content of calcium phosphate becomes particularly evident when expressed in terms of ratios between the number of patients in group R and the number of patients in group S for each stone category (Table 2). The mean ratio increased from 1.17 to 14.0 as the phosphate content increased. The mean ratio was 1.2 in patients with either CaOx or CaOx(CaP) stones, and 2.0 in patients with CaOxCaP and CaP(CaOx) stones.

Table 4. Urine composition in 68 men with recurrent stone disease (group R) and 45 men with a history of only one stone (group S)

Urine variable	Group R	Group S	Significance of difference
Calcium (mmol/24 h)	7.28 (3.09)	6.60 (2.49)	$P > 0.10$
Oxalate (mmol/24 h)	0.30 (0.12)	0.31 (0.08)	$P > 0.10$
Citrate (mmol/24 h)	2.51 (1.05)	2.88 (1.20)	$0.05 < P < 0.10$
Magnesium (mmol/24 h)	4.79 (1.49)	4.60 (1.99)	$P > 0.10$
Volume (l/24 h)	1.62 (0.49)	1.57 (0.59)	$P > 0.10$
AP(CaOx) index	1.28 (0.84)	1.26 (0.52)	$P > 0.10$
AP/(CaOx) index (s)	1.33 (0.76)	1.23 (0.43)	$P > 0.10$

Values are mean (SD)

Table 5. Urine composition in 40 women with recurrent stone disease (group R) and 19 women with a history of only one stone (group S)

Urine variable	Group R	Group S	Significance of difference
Calcium (mmol/24 h)	6.45 (3.38)	4.59 (2.24)	$P < 0.05$
Oxalate (mmol/24 h)	0.28 (0.10)	0.27 (0.10)	$P > 0.10$
Citrate (mmol/24 h)	2.51 (1.31)	2.63 (1.68)	$P > 0.10$
Magnesium (mmol/24 h)	4.22 (1.57)	2.73 (1.41)	$P < 0.001$
Volume (l/24 h)	1.49 (0.59)	1.32 (0.60)	$P > 0.10$
AP(CaOx) index	1.27 (0.60)	1.11 (0.59)	$P > 0.10$
AP/(CaOx) index (s)	1.23 (0.70)	0.93 (0.55)	$P > 0.10$

Values are mean (SD)

Table 6. Urine composition and age in relation to stone composition in men

Stone composition:	CaOx	CaOx(CaP)	CaOxCaP	CaP(CaOx)
N°. of patients:	36	51	30	7
Age (years)	63 (10)	55 (10)	54 (11)	60 (14)
Calcium (mmol/24 h)	4.96 (2.29)	7.36 (2.67)[a]	8.61 (2.74)[a]	7.50 (3.65)[b]
Oxalate (mmol/24 h)	0.28 (0.12)	0.29 (0.10)	0.32 (0.10)	0.32 (0.11)
Citrate (mmol/24 h)	2.46 (1.13)	3.06 (1.18)[c]	2.40 (0.94)	1.94 (0.65)
Magnesium (mmol/24 h)	4.33 (1.89)	4.80 (1.66)	4.84 (1.60)	5.47 (1.79)
Volume (l/24 h)	1.46 (0.57)	1.66 (0.54)	1.63 (0.55)	1.72 (0.52)
AP (CaOx) index	1.05 (0.48)	1.17 (0.62)	1.69 (1.02)[d]	1.41 (0.67)[a]
AP(CaOx) index (s)	1.00 (0.43)	1.22 (0.56)	1.72 (0.78)[a]	1.55 (0.82)[b]

Values are mean (SD)
[a] $P < 0.001$ vs CaOx
[b] $P < 0.02$ vs CaOx
[c] $P < 0.05$ vs CaOx
[d] $P < 0.01$ vs CaOx

Table 7. Urine composition and age in relation to stone composition in women

Stone composition:	CaOx	CaOx(CaP)	CaOxCaP	CaP(CaOx)
N°. of patients:	14	15	21	9
Age (years)	63 (8)	62 (10)	50 (15)	56 (12)
Calcium (mmol/24 h)	4.87 (2.37)	6.41 (4.19)	6.84 (2.76)[a]	5.03 (2.90)
Oxalate (mmol/24 h)	0.31 (0.10)	0.25 (0.08)	0.31 (0.10)	0.23 (0.08)[a]
Citrate (mmol/24 h)	2.33 (1.18)	2.63 (1.83)	2.74 (1.38)	2.66 (1.34)
Magnesium (mmol/24 h)	3.36 (1.51)	3.58 (1.31)	4.07 (1.99)	4.09 (1.42)
Volume (l/24 h)	1.54 (0.51)	1.34 (0.70)	1.51 (0.65)	1.29 (0.40)
AP(CaOx) index	1.12 (0.52)	1.35 (0.72)	1.43 (0.48)	0.92 (0.54)
AP(CaOx) index (s)	1.14 (0.63)	1.07 (0.61)	1.40 (0.70)	0.76 (0.41)

Values are mean (SD)
[a] $P < 0.05$ vs CaOx

Table 8. Urine variables in patients (men and women) with CaOx and CaOx(CaP) stones and in those with CaOxCaP and CaP(CaOx) stones

Urine variable	CaOx + CaOx(CaP)	CaOxCaP + CaP(CaOx)	Significance of difference
Calcium (mmol/24 h)	6.16 (2.95)	7.32 (3.19)	$P < 0.05$
Oxalate (mmol/24 h)	0.29 (0.11)	0.30 (0.11)	$P > 0.10$
Citrate (mmol/24 h)	2.72 (1.28)	2.47 (1.17)	$P > 0.10$
Magnesium (mmol/24 h)	4.31 (1.75)	4.47 (1.85)	$P > 0.10$
Volume (l/24 h)	1.54 (0.57)	1.51 (0.58)	$P > 0.10$
AP(CaOx) index	1.15 (0.57)	1.46 (0.80)	$P < 0.01$
AP(CaOx) index (s)	1.12 (0.54)	1.45 (0.76)	$P < 0.01$

As is evident from Table 3 there were no major differences in sex distribution between groups R and S, but as could be expected there were more women among the patients who had formed stones with a high content of calcium phosphate.

Urine composition in men and women from groups S and R (Tables 4, 5) showed no differences in oxalate and citrate excretion, but women from group R had a significantly ($P < 0.05$) higher excretion of calcium than women from group S. Although a numerically higher mean calcium excretion also was observed in men from group R in comparison with men from group S, this difference was not statistically significant. Women in group R also had a higher magnesium excretion than women in group S.

A comparison of urine composition in relation to stone composition in men (Table 6) showed that calcium excretion was significantly higher in patients with CaOx-(CaP), CaOxCaP and CaP(CaOx) stones than in patients with pure CaOx stones. Urinary citrate was significantly ($P < 0.05$) higher in association with CaOx(CaP) stones than CaOx stones. There were, however, no differences in terms of urinary oxalate and magnesium or urine volume. In women (Table 7) the only significant differences were a higher calcium excretion in CaOxCaP stone formers and a lower oxalate excretion in association with CaP(CaOx) stone formation. In Table 8 urine composition in patients (both men and women) with CaOx and CaOx(CaP) stones is compared with that in patients who had formed stones composed of CaOxCaP and CaP(CaOx). The latter group had significantly higher levels of calcium ($P < 0.05$), AP(CaOx) index ($P < 0.01$) and AP(CaOx) index (s) ($P < 0.01$).

Discussion

In this retrospective study we used data on stone and urine composition from a consecutive group of idiopathic calcium oxalate stone formers treated with extracorporeal shock wave lithotripsy. The main reason for studying such a subgroup of patients was that all of them had a stone analysis carried out on the gravel that passed after the lithotripsy. This is in contrast to the situation in most other populations of stone patients in whom passed stones are lost surprisingly frequent. Furthermore all these patients had a 24-h urine collection analysed before the treatment for risk factors of calcium oxalate stone formation, irrespective of their previous stone history. Studies with repeated urinalysis have shown that urine composition is not significantly altered by the shock wave lithotripsy with removal of stone material from the kidney [34].

Although a great deal of information has accumulated on the different factors that contribute to and modify the crystallization process in urine, the major events that result in the formation of a calcium stone are still poorly understood. The majority of calcium stones contain calcium oxalate, and an increased excretion of calcium is a common finding in these patient [23, 27, 28]. A slight hyperoxaluria is also often recorded and the powerful influence of oxalate on the crystallization has been emphasized [12, 26, 30]. It is important to realize, however, that a greater number of calcium stones are composed of mixtures of calcium oxalate and calcium phosphate, and in a recent report [22] the use of sensitive analytical methods disclosed that phosphate was a surprisingly common constituent of small calcium stones. Furthermore, the formation of pure calcium oxalate stones appeared to be associated with a urine composition different from that observed in patients with mixed stones. In extensive X-ray crystallographic studies Leusmann [18] found that the recurrence rate was highest for stones composed of brushite (calcium hydrogen phosphate). Long-term follow-up of patients after extracorporeal shock wave lithotripsy also indicated that those who formed new stones during the first 4 years had previously very often formed stones with a high content of calcium phosphate [34]. It therefore appears essential to consider not only the crystallization of calcium oxalate but also that of calcium phosphate in patients forming stones containing mixtures of these two salts [16, 20, 21].

The most interesting observation in this series of patients was that a higher content of calcium phosphate in the stones appeared to be associated with a more serious stone disease in terms of recurrences. Either previous history of stone formation or more than one stone in the renal tract at the time of treatment was frequently observed in patients with more than 25% calcium phosphate in their stones. These results thus support the assumption that calcium phosphate is an important crystal phase in patients with recurrent calcium stone formation. The possible role of calcium phosphate in the form of brushite was suggested many years ago [20, 23–25], but a general acceptance of this hypothesis has so far

not been obtained because of the infrequent occurrence of brushite in renal stones.

In terms of urine composition there was a significantly higher excretion of calcium in male patients who had produced stones containing calcium phosphate in comparison with patients who had pure CaOx stones. Women with CaOxCaP stones also had a significantly higher calcium excretion than CaOx stone formers. When all patients with stones containing more than 25% calcium phosphate [CaOxCaP and CaP(CaOx)] were compared with those who either had no or only a small amount of calcium phosphate in their stones [CaOx and CaOx-(CaP)], there was a significantly higher excretion of calcium in the former group. This apparently resulted in significantly higher values of both the AP(CaOx) index and the AP(CaOx) index (s). This does not, however, indicate only an increased risk of calcium oxalate crystallization in these patients but also certainly an increased risk of calcium phosphate crystallization provided the pH level is favourable for such a precipitation. On the basis of direct measurements in whole urine samples a close relationship was previously demonstrated between the crystallization risks of calcium oxalate and calcium phosphate [31]. Unfortunately the way in which urine was collected from patients in the present investigation made it impossible to calculate the ion-activity products of different calcium phosphate salts. Urinary phosphate was not included in our analytical programme at the time these patients were examined, and the acidification of the urine excluded determination of pH.

When urine composition was compared between patients from group R and from group S the only significant difference was a higher calcium excretion in female recurrent stone formers. A slightly higher mean calcium excretion level was also observed in men with recurrent stone disease, but a significant difference was not found. Neither urinary oxalate nor citrate were different between these groups and it is therefore possible that there is a periodic high risk of calcium phosphate precipitation, either as brushite at low pH [20, 25] or as hydroxyapatite at higher pH levels.

Differences in other crystallization variables such as inhibitors of crystal growth and crystal aggregation might certainly also contribute to differences between recurrent and non-recurrent stone formers as well as between patients forming stones of different composition. It is thus possible that the higher citrate excretion in male patients with CaOx(CaP) stones might have reduced the rate of calcium phosphate precipitation and thereby the recurrence rate despite the high calcium excretion in this group. Other measurements on the inhibition or promotion of crystallization in the different urines were not carried out in these patients.

There are several ways in which calcium phosphate can theoretically contribute to augmented stone formation. It might secondarily precipitate on nuclei of calcium oxalate and thereby cause a rapid growth of such crystals during periods of increased calcium phosphate supersaturation. Several authors accordingly claim that crystals of calcium oxalate constitute the nucleus of most calcium-oxalate-containing stones [5, 14, 15, 19]. The heterogenous crystallization of calcium phosphate on calcium oxalate might be necessary for the creation of crystals of sufficient size to start the development of a stone. Unfortunately neither calcium oxalate monohydrate nor dihydrate have a crystal surface favourable for calcium phosphate crystallization [16], and only the trihydrate appears to play a role in this respect. Calcium oxalate trihydrate is, however, an unstable crystal phase not frequently observed in renal stones. Another possibility is that calcium phosphate either as brushite or as hydroxyapatite constitutes the initial crystal phase on which calcium oxalate is secondarily deposited [1, 3, 9–11, 21, 24, 36]. The existence of such a mechanism is supported by the fact that calcium oxalate can easily grow on a calcium phosphate crystal surface [4, 20] and by the constant supersaturation of urine with both substances [23, 27]. It is also theoretically attractive to assume a primary precipitation of calcium phosphate in view of the supersaturation levels in the renal tubular system [8; Tiselius, unpublished data]. Recent microscopic examination of urine demonstrated that amorphous phosphate was also the most frequent crystal type in urine [13]. Crystals of calcium phosphate can probably also form bridges between many small calcium oxalate crystals or crystal aggregates and in this way rapidly build up large concretions. Co-precipitation of calcium oxalate and phosphate at high pH levels was observed by Hallson and Rose [11].

The conclusion from the results of this investigation is that information on the content of calcium phosphate in the stone material, together with data from analysis of urine composition, might be helpful in predicting stone recurrences. Estimates of calcium oxalate and calcium phosphate supersaturation levels [30–33], as well as direct determination of their crystallization properties during particular risk periods, would certainly also be of great value. This requires, however, analysis of urinary phosphate and pH. Further prospective studies are in progress to determine the usefulness of such a system for evaluation of patients with calcium oxalate stone disease.

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