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Risk formulas in calcium oxalate urolithiasis

Abstract In order to reflect the risk of calcium stone formation, risk formulas have been described in the literature with the objective of being able to predict the further course of the stone disease. Some of these formulas are reviewed in this paper. Various results were obtained when different risk expressions were related to the severity of the stone disease. Although a reliable prediction of the future course of the disease most certainly cannot be made by analysis of the variables included in these expressions, several of the risk formulas differed significantly between patients with and without recurrent stone formation during a reasonable follow-up period. Some risk formulas might thus be helpful, at least to some extent, in selecting those patients in whom continuous stone formation can be anticipated and in whom active therapeutic measures should be beneficial and worthwhile. With an increased understanding of the mechanisms of calcium oxalate stone formation and our possibilities of measuring the relevant risk factors, it is likely that improved risk formulas with an increased predictive power can be developed. Until this becomes a reality, in most cases we have to combine important information on the history and clinical observations of the disease with a risk formula that offers a high degree of discrimination with respect to the risk of further stone formation.

The optimal care of patients with renal stone disease should include measures for prevention of recurrent stone formation. The recurrence rate in patients with calcium stone disease is generally considered to be high, but it is also known that there is pronounced variation among stone formers in the course of their disease. Whereas some patients thus might benefit from a specific therapeutic action, this will be obviously unnecessary in others. To achieve the goal of giving the individual patient an appropriate form of therapy, the approach has to be selective in two ways. First, it is necessary to find patients at particular risk of stone formation and secondly, when this has been done, to identify and possibly eliminate risk factors responsible for or contributing to the stone formation. Although it is usually easy to make a therapeutic decision in patients with a history of frequent or severe stone formation, the ideal goal should be a method that allows identification of these patients at an early stage of their disease, thereby avoiding unnecessary suffering for the patient and expense to the health care system.

The development of calcium stones is a symptom of increased crystallization of calcium oxalate (CaOx), calcium phosphate (CaP) or both. A fundamental prerequisite therefore is a sufficient supersaturation with any of these crystal phases, either in the final urine or at any relevant level of the nephron where the initial crystallization might take place [23, 40]. In as much as CaOx is the major constituent of the vast majority of calcium stones, most attention has been directed at the crystallization propensity of this salt. A urine supersaturated with CaOx to a metastable level can thus result in heterogeneous nucleation as well as crystal growth [16]. There is overwhelming evidence that urine contains efficient inhibitors of these processes as well as of the aggregation of crystals [21]. In addition, the crystallization can be augmented by promoters and by less well understood factors that cause retention of crystals. It is also important to note that CaP probably plays a significant role in the development of many CaOx-containing stones [1, 4, 19, 23, 46].

Although the formation of a CaOx stone is the result of a complex and incompletely understood sequence of events, it is nevertheless believed that the crystallization properties are at least partly reflected in the composition of voided urine. This being the case, any imbalance

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between the driving force of the supersaturation and the action of inhibitors might be revealed by analysis of the constituents and crystallization properties in urine samples.

The most important determinants for supersaturation with CaOx are: oxalate, calcium, citrate and magnesium, and for supersaturation with CaP: pH, calcium, phosphate and citrate [33, 35, 37, 40]. In addition, citrate has been shown to inhibit growth and aggregation of both CaOx and CaP crystals. The growth of CaP crystals is also inhibited by magnesium. A major part of the inhibition of CaOx crystal growth and of CaOx and CaP crystal aggregation is, however, considered to be accomplished by different macromolecules in urine [21].

For evaluation of the net crytallization properties in urine, a combination of different risk factors is assumed to be more informative than the level of individual variables in a set of analyses. The influence of an excessive excretion of one urine variable might thus be attenuated by a high or a low excretion of another. This has been the rationale for the development of various risk formulas, risk quotients and risk indices. Although there is a lot of evidence that such risk expressions are higher in stone formers than in normal subjects, all formulas suffer from the drawback of a more or less pronounced overlap between the two groups. This is of minor importance when the risk formula is used to compare pretreatment with treatment periods. To predict the future risk of stone formation, however, it is important that the level of the risk formula reflects the severity of the disease, or at least the risk of forming more stones. It is commonly taken for granted that abnormal findings in urine composition are closely associated with the risk level of stone formation, but there is an astonishing paucity of work in the literature providing support for such an assumption.

In addition to analysis of urinary risk factors, the risk of crystallization in urine can be directly assessed with different techniques. This topic is discussed in detail in another paper in this issue.

The present paper summarizes literature data on a number of risk formulas that have been proposed for use in patients with CaOx stone disease. In addition, urine data from our own patients have been revisited and used to compare some of the risk expressions with observations on the course of the disease.

Calcium/magnesium ratio

Because of the important role of calcium in supersaturation with both CaOx and CaP and also the inhibiting and chelating properties of magnesium, the calcium/magnesium and the magnesium/calcium ratios have been commonly used to express the risk situation [41]. With few exceptions a higher calcium/magnesium ratio among stone-formers is a consistent finding in the literature [11, 13, 43]. In as much as a low urinary magnesium is observed only infrequently in stone formers, the calcium/magnesium ratio merely reflects the degree of hypercalciuria, with the advantage of being a better standardized measure than calcium alone.

Oreopoulos et al. [25] observed that a patient with recurrent stone formation after parathyroidectomy had a calcium/magnesium ratio that returned to the pretreatment level, in contrast to those who remained stone free. Following several other early reports on the usefulness of the calcium/magnesium ratio in the evaluation of stone formers [9, 11, 18, 22, 43, 50], it was frequently used to monitor the therapeutic effect, particularly when thiazides were administered. In the long-term studies with hydrochlorothiazide reported by Yendt [50] a remarkable reduction in the recurrence rate was associated with decreased calcium/magnesium levels. In our own experience the recurrence-preventive effect of 2.5 mg of bendroflumethiazide per day was inferior to that of a daily dose of 5 mg, and the reduction of the calcium/magnesium ratio was greater in the latter group [2, 3].

When the calcium/magnesium ratios in our own 24-h urine samples were compared between patients with and without recurrent stone formation during the period following the biochemical evaluation, significantly higher values were recorded in both men and women with recurrent stone formation (Tables 1, 2).

In another study comprising 93 patients with calcium stone disease, Laerum [20] could not show any association between the calcium/magnesium ratio and the frequency of stone formation.

Table 1 Different risk expressions calculated from analytical findings in 24-h urine from male patients with and without recurrent stone formation during follow-up

Mean (SD) number	Recurrent stone formation	No recurrent stone formation	*P*-value
Calcium/magnesium	1.83 (0.88) 128	1.59 (0.75) 318	< 0.01
Calcium/citrate	3.96 (2.40) 138	3.23 (3.40) 595	< 0.02
Parks and Coe score	0.967 (0.517) 111	0.800 (0.525) 254	< 0.01
$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Citrate}}$	0.41 (0.87) 128	0.30 (0.47) 318	> 0.05

Table 2 Different risk expressions calculated from analytical findings in 24-h urine from female patients with and without recurrent stone formation during follow-up

Mean (SD) number	Recurrent stone formation	No recurrent stone formation	*P*-value
Calcium/magnesium	1.87 (0.71) 46	1.54 (0.71) 168	< 0.01
Calcium/citrate	4.21 (5.59) 49	2.97 (4.48) 289	> 0.05
Parks and Coe score	2.240 (1.197) 40	1.757 (1.227) 152	< 0.05
$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Citrate}}$	0.46 (0.96) 46	0.28 (0.36) 168	< 0.05

When the risk of CaOx crystallization, as assessed by titration with sodium oxalate [36], was compared with calcium/magnesium ratios in the same urine samples, the coefficient of correlation was 0.56 in normal urine ($P = 0.003$) and 0.68 in urine from stone formers ($P < 0.001$).

Calcium/citrate ratio

With increased knowledge of the important role of citrate in the calcium salt crystallization and the great power of citrate to form soluble complexes with calcium, the use of the calcium/citrate ratio has become widespread [44]. One contribution to the popularity of this method of risk estimation has been the presently very common use of alkaline citrate in the stone-preventive treatment. The calcium/citrate ratio is particularly interesting because it includes the two urine variables that have most frequently been reported to differ between stone formers and normal subjects. This quotient might also reflect the relative risk of crystallization not only with CaOx, but also with CaP [44].

Not surprisingly the calcium/citrate ratios are usually higher in stone formers than in normal subjects [40], and as expected the ratio is reduced during treatment with alkaline citrate. In a previously published comparison of stone formers with and without recurrences during follow-up [5] the mean (SD) calcium/citrate ratio was 3.24 (2.31) in the former and 2.13 (1.19) in the latter group. There was a positive correlation ($r = 0.55; P = 0.004$) between the calcium/citrate ratio and the direct assessment of the risk of CaOx crystallization.

Hauser et al. [15] reported in a short-term study (12 months) a frequency of recurrent stone formation of 5.7% in patients treated with alkaline citrate, as against 67% in an untreated group. In the former patients the mean (SD) calcium/citrate ratio was reduced from 6.25 (5.73) to 1.97 (1.51) and in the latter, from 6.31 (10.82) to 6.07 (11.48). This group recorded a mean (SD) calcium/citrate ratio of 1.85 (0.93) in normal subjects and 2.53 (1.97) in single-stone formers. From these observations it was concluded that the calcium/citrate ratio was lowest in normal subjects, slightly higher in single-stone formers and much higher in recurrent stone formers. There was also a relationship between the calcium/citrate ratio and the frequency of recurrent stone formation.

Calculation of the calcium/citrate ratio in 24-h urine samples from a large group of calcium stone formers disclosed significantly higher values in male patients with recurrent stone formation during the period that followed the biochemical evaluation (Table 1). In female stone formers the mean calcium/citrate ratio was also numerically higher in the group with recurrences, but because of wide variation the difference did not reach the level of statistical significance (Table 2).

These findings thus show that the calcium/citrate ratio to some extent reflects the severity of the disease, at least in male patients, an observation that is also emphasized by the calcium/citrate ratios in 16-h urine shown in Tables 5 and 6.

By applying discriminant analysis, Parks and Coe [26] were able to formulate a discriminant score based on the analysis of calcium and citrate only. With these scores they were able to discriminate between stone formers and normal subjects in a much better way than when individual urine variables were used. They also observed that treatment resulted in reduced, though not normalized, scores. The prospective value of these scores was not analysed however, and neither was its relationship with the activity of the stone disease.

These score formulas were applied to the calcium and citrate excretion in a group of stone formers in whom data on the history and course of the disease were available. The scores were calculated for male and female stone formers according to the relationship given below, in which the concentrations of calcium (C_{Ca}) and citrate (C_{Cit}) were obtained from the 24-h excretion (mmol) in a standardized volume of 1.5 l:

Parks and Coe score for men

$$= 0.250 \cdot C_{Ca} - 0.885 \cdot C_{Cit} + 0.879$$

Parks and Coe score for women

$$= 0.821 \cdot C_{Ca} - 1.052 \cdot C_{Cit} + 0.224$$

This is not exactly in accordance with the original score formulas, but the fixed 24-h volume was used to make the scores comparable with other standardized expressions discussed in this paper.

Significantly higher standardized Parks and Coe scores were recorded in urine from both male and female patients who developed new stones during the period following the biochemical evaluation than in urine from patients who did not (Tables 1, 2).

Saturation–inhibition index

In order to account fully for the balance between the supersaturation with CaOx and the inhibiting potential of urine, Robertson et al. [28] presented convincing evidence for the use of a saturation–inhibition index. This index was derived from computerized calculation of the ion-activity product of CaOx and the inhibition as assessed by crystal recording in a Coulter counter following addition of seed crystals to a solution metastably supersaturated with CaOx. The saturation–inhibition index offered very good discrimination between stone formers and normal subjects and was obviously related to the frequency of stone formation. Although the factor of inhibition in this index reflects the effects of diluted urine on both crystal growth and crystal aggregation the saturation–inhibition index has not been commonly used by other authors. The reasons for this are probably both the great number of urine analyses required for calculating the saturation level and the necessity of

assessing the inhibiting properties. Although it is evidently a valuable tool for discrimination between different subgroups of stone formers, the complex construction of the saturation–inhibition index apparently made it less attractive for use in routine clinical work.

Other simple quotients

Although both the calcium/magnesium and the calcium/citrate ratios have proved to be useful in the evaluation of stone formers, they are both invalidated by the fact that the excretion of oxalate was not accounted for. In an attempt to compensate for this short-coming the following quotients were calculated in 24-h urine from stone formers and normal subjects:

$$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Creatinine}}$$

$$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Creatinine} \times Inh_{GR}}$$

$$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Creatinine} \times Inh_{GR}}$$

in which Inh_{GR} represents the inhibition of CaOx crystal growth in dilute urine. As previously reported, all these quotients were higher in 24-h urine from stone formers than from normal subjects [34, 43]. A relationship with the severity of stone disease was studied in a limited series of patients [32], whereby increased levels of the quotient [calcium × oxalate/magnesium × creatinine] were associated with a higher frequency of stone formation as well as with a larger stone burden. The inclusion of urate in expressions of this type did not result in better discrimination between single and recurrent stone formers.

Because of the subsequent development of other risk quotients, a more extensive study of the clinical value of the quotients referred to have not been carried out. When the quotient:

$$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Citrate}}$$

was recalculated from 24-h urine data in our stone formers, numerically higher values were recorded in stone formers with new stone formation during the follow-up period than in stone formers without, but as is evident from Tables 1 and 2 the difference was statistically significant only in women. When the latter risk quotient was compared with a direct assessment of the CaOx crystallization risk [36], the coefficient of correlation was 0.46 ($P = 0.017$) in urine from normal subjects and 0.51 ($P = 0.001$) in urine from stone formers.

In male patients the urinary calcium/oxalate quotient was higher both in 70 first-time stone formers than in 470 recurrent stone formers ($P < 0.05$), and in 142 patients who developed new stones during the follow-up period than in 606 who did not ($P < 0.001$). No such differences were recorded in female stone formers.

Probability index

On the grounds that calcium, oxalate, pH, glycosaminoglycans and urate were the factors of greatest importance for discrimination between normal subjects and stone formers, an ingenious method for predicting the risk of stone formation was devised by Robertson et al. [29]. They derived a probability index (P_{SF}) by combining the relative risk of having urine with an abnormal composition regarding the mentioned urine variables. P_{SF} allowed the authors to discriminate between stone formers and normal subjects in an excellent way. Women and children had lower P_{SF} values than normal men, and the P_{SF} values in single-stone formers were lower than in recurrent stone formers. It was also shown that P_{SF} was related to the frequency of stone formation.

Ryall et al. [31] analysed the same variables in 24-h urine from a group of normal and stone-forming men. Although they found that a higher proportion of stone-forming than normal men had an oxalate excretion above the 95th percentile, they could not demonstrate any differences between the two groups and were thus unable to calculate a meaningful P_{SF}. From this and a previous study [30], they came to the conclusion that analysis of urine composition with reference to these variables had no predictive value. The absence of differences in urine composition between stone formers and normal subjects, particularly in terms of urinary calcium, are, however, infrequently encountered in the literature.

Although the P_{SF} index, at least in the hands of its inventors, provided a valuable tool for prediction of further stone formation, the factors included in the index can be discussed. In our own population of stone formers hyperuricosuria was not a common finding [43], and this has been supported by several other groups [12, 13, 48]. Furthermore, the role of glycosaminoglycans as a modifier of the crystallization process might be overestimated. The technique applied for development of P_{SF} can, however, probably be used to formulate other expressions containing the most appropriate risk factors.

Ion-activity product index

In view of the important role of supersaturation in the deposition of both CaOx and CaP, simplified estimates were derived based on the excretion of calcium, oxalate, citrate and magnesium and the urine volume for CaOx and calcium, phosphate, pH, citrate and volume for CaP. In a 24-h urine sample the corresponding indices were given the following forms [33, 35, 38]:

$$AP(\text{CaOx})\ \text{index} = \frac{1.9 \cdot \text{Calcium}^{0.84} \cdot \text{Oxalate}}{\text{Citrate}^{0.22} \cdot \text{Magnesium}^{0.12} \cdot \text{Volume}^{1.03}}$$

Table 3 AP(CaOx) $index_s$ in 24-h urine from male patients with calcium oxalate stone disease

Subgroup	Mean SD number	Subgroup	Mean SD number	*P*-value
Single-stone formers	1.33 0.83 68	Recurrent-stone formers	1.61 0.85 453	< 0.02
Number of stones ≤ 2	1.72 0.70 31	Number of stones ≥ 3	1.71 0.88 189	> 0.05
No stones during follow-up	1.47 0.78 590	New stones during follow-up	1.72 0.84 137	< 0.001
No stones during a follow-up period of at least 5 years	1.48 0.71 109	New stones during a follow-up period of at least 5 years	1.78 0.81 97	< 0.01
No growth of stones during a follow-up period of at least 5 years	1.57 0.86 18	Growth of stones during a follow-up period of at least 5 years	1.76 0.68 60	> 0.05
$f_{SF}^{a} < 0.15$	1.82 0.89 49	$f_{SF} \geq 0.15$	1.65 0.89 103	> 0.05
SAI[b] < 5	1.53 0.60 29	SAI ≥ 5	1.73 0.78 111	> 0.05

[a]Frequency of stone formation during the period before the biochemical evaluation
[b]Stone age index = number of stones/patient's age at the time of biochemical evaluation

$$AP(\text{CaP}) \text{ index} = \frac{2.7 \cdot 10^{-3} \cdot \text{Calcium}^{1.07} \cdot \text{Phosphate}^{0.70} \cdot (\text{pH} - 4.5)^{6.8}}{\text{Citrate}^{0.20} \cdot \text{Volume}^{1.31}}$$

In as much as a reliable pH is difficult to obtain, a standardized AP(CaP) index [AP(CaP) $index_s$] was obtained for a pH of 7 and a 24-h urine volume of 1.5 l, whereas the AP(CaOx) $index_s$ was obtained by setting the volume at 1.5 l. The levels of the AP(CaOx) index and the AP(CaOx) $index_s$ in patients with and without recurrences during a follow-up period have already been published [42]: we found lower values in urine from male patients who remained stone free during an average follow-up period of 5 years than in those who continued to form stones. The reduced supersaturation with CaOx was associated with the therapeutic effect of different pharmacological agents. In Table 3 and 4 the updated results of analysis of 24-h urine composition in our stone formers, subgrouped according to clinical observations, are summarized. In an attempt to express the severity of the disease a stone age index (SAI) was computed as the quotient between the total number of stones and the patient's age at the time of the biochemical evaluation.

As shown in Table 3, AP(CaOx) $index_s$ derived from male 24-h urine was significantly higher in patients with recurrent stone disease than in patients who had formed only one stone ($P < 0.02$). There was also a higher AP(CaOx) $index_s$ in patients who continued to form new stones during the follow-up period, both totally ($P < 0.001$) and when only those patients were considered who had a follow-up period of at least 5 years ($P < 0.01$). Also a higher AP(CaOx) index was recorded in patients with recurrent stone formation during the follow-up period.

There were, however, no differences in AP(CaOx) $index_s$ or AP(CaOx) index that could be related to differences in the number of stones formed, the frequency of stone formation, the SAI level or the growth of residual fragments or stones. Neither were there any differences in 24-h AP(CaP) $index_s$ that could be related to the severity of the disease.

Table 4 summarizes the recorded AP(CaOx) $index_s$ values in 24-h urine from female stone formers. The AP(CaOx) $index_s$ was significantly higher in women with recurrent stone formation during the follow-up period, and also higher in patients who demonstrated stone growth during this period. A higher AP(CaOx) $index_s$ was also recorded in patients who had formed more than two stones than in those who had formed only one or two stones. No differences in terms of AP(CaOx) $index_s$ were recorded between first-time and recurrent stone formers or between patients with different SAI levels or frequencies of stone formation, but the AP(CaOx) $index_s$ was higher in women with severe than in those with mild recurrent disease. A similar pattern was recorded in the case of the AP(CaOx) index.

The cumulative frequency distributions of the AP (CaOx) $index_s$ in male and female stone formers with and without recurrent stone formation as shown in Fig. 1. It is evident from these graphs that although the distributions are different in the two groups, the future course of the disease cannot be predicted from an individual's AP(CaOx) index level. The value only indicates the relative probability of the risk of becoming a recurrent stone former.

Table 4 AP(CaOx) $index_s$ in 24-h urine from female patients with calcium oxalate stone disease

Subgroup	Mean SD number	Subgroup	Mean SD number	*P*-value
Single-stone formers	1.06 0.49 41	Recurrent-stone formers	1.18 0.63 217	> 0.05
Number of stones ≤ 2	0.97 0.51 25	Number of stones ≥ 3	1.45 0.75 63	< 0.01
No stones during follow-up	1.13 0.58 288	New stones during follow-up	1.44 0.76 49	< 0.001
No stones during a follow-up period of at least 5 years	1.10 0.61 77	New stones during a follow-up period of at least 5 years	1.63 0.77 33	< 0.001
No growth of stones during a follow-up period of at least 5 years	1.36 0.42 11	Growth of stones during a follow-up period of at least 5 years	1.91 0.76 19	< 0.05
$f_{SF} < 0.15$	1.01 0.57 9	$f_{SF} \geq 0.15$	1.36 0.72 33	> 0.05
SAI < 5	1.16 0.60 299	SAI ≥ 5	1.28 0.74 38	> 0.05

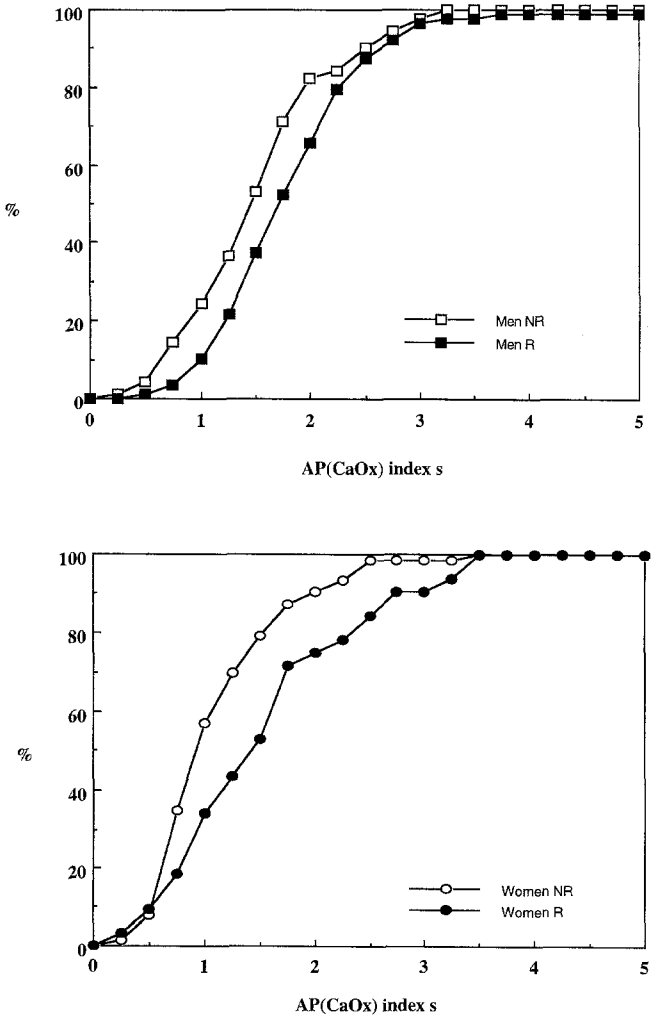

Table 5 Biochemical findings in 16-h urine from male patients with calcium oxalate-containing stones and low or high SAI

Parameter	SAI < 5 mean (SD) *n*	SAI ≥ 5 mean (SD) *n*	*P*-value
AP(CaOx) index	1.87 (0.97) 33	1.94 (1.05) 33	> 0.05
AP(CaOx) $index_s$	1.67 (0.73) 33	2.13 (0.91) 34	< 0.05
AP(CaP) $index_s$	51.5 (29.9) 34	70.2 (39.0) 34	< 0.05
Calcium/citrate	2.43 (1.00) 34	3.09 (1.50) 34	< 0.05

When the composition of 16-h urine from male patients with an SAI of less than 5 at the time of the biochemical evaluation was compared with that in urine from patients with an SAI of 5 or more, AP(CaOx) $index_s$, AP (CaP) $index_s$ and calcium/citrate ratios, but not AP(CaOx) index, were significantly higher in the latter group (Table 5). Female patients with an SAI of at least 5 had a significantly higher level of calcium/citrate (Table 6).

Marangella et al. [24] and Trinchieri [47] were not able to demonstrate any differences in urine composition or supersaturation with CaOx or brushite between first-time

Fig. 1 Cumulative frequency distribution curves for AP(CaOx) $index_s$ in male patients (*above*) with (*R*) and without (*NR*) recurrent stone formation and in female patients (*below*) with (*R*) and without (*NR*) recurrent stone formation during the period following the biochemical evaluation

Table 6 Biochemical findings in 16-h urine from female patients with calcium oxalate-containing stones and low or high SAI

Parameter	SAI < 5 mean (SD) *n*	SAI ≥ 5 mean (SD) *n*	*P*-value
AP(CaOx) index	1.41 (0.88) 22	1.48 (0.81) 23	> 0.05
AP(CaOx) $index_s$	1.59 (0.94) 22	1.46 (0.68) 23	> 0.05
AP(CaP) $index_s$	46 (27) 22	66 (52) 22	> 0.05
Calcium/citrate	1.97 (1.40) 22	3.12 (2.10) 23	< 0.05

and recurrent stone formers, but it is noteworthy that the previous authors found the numerically highest values among recurrent stone formers. Högbarth et al. [17] concluded from a long-term follow-up of 49 patients that repeated analysis of 24-h urine had no predictive value for the risk of stone recurrences, but no risk indices were calculated.

Other indices aimed at expressing the supersaturation have been reported elsewhere in the literature. Although related to the crystallization propensity, their superiority in reflecting the stone risk has not been documented.

Quatients between ion-activity product indices and crystallization inhibition

In a similar way to the saturation-inhibition index [28], quotients between the AP(CaOx) index and the inhibition of CaOx crystal growth (Inh_{GR}) and/or aggregation (Inh_{AGG}), were shown to be powerful tools for discrimination between stone formers and normal subjects [45]. The quotient AP(CaOx) index/Inh_{AGG} was the most interesting of these expressions, inasmuch as the difference between stone formers and normal subjects in Inh_{GR} was small and probably of minor clinical importance. Owing to methodological improvements in assessing Inh_{AGG} it has so far not been possible to relate the AP(CaOx) index/Inh_{AGG} to the clinical course of the disease in a large group of stone formers, because of insufficient duration of the follow-up period. Nevertheless, in a limited comparison of 17 patients who developed new stones after the evaluation and 25 who did not, higher risk quotients were observed in the previous group. A quotient $100 \cdot$ AP(CaOx) index/Inh_{AGG} above 2.0 was recorded in 76% of the patients with recurrent stone formation, but in only 52% of the non-recurrent stone formers. No patient with a risk quotient below 1.0 was found in the recurrence group. For the quotient $10^4 \cdot$ AP(CaOx) index/[$Inh_{AGG} \cdot Inh_{GR}$] a value above 4.0 was recorded in 53% and 46% of recurrent and non-recurrent stone formers, respectively. Direct assessment of the crystallization risk in terms of CaOx-CR [38] resulted in values above 1.0 in 82% of the recurrent and 68% of the non-recurrent stone formers, and the quotient $100 \cdot$ CaOx-CR/Inh_{AGG} was above 1.5 in 88% of the patients with new stone formation, compared with 65% in those without. It needs to be emphasized, however, that better biochemical discrimination can hopefully be expected with a longer follow-up period, because several patients who in this comparison were classified as non-recurrent stone formers will probably later turn out to be recurrent stone formers.

The quotients $100 \cdot$ AP(CaOx)index/Inh_{AGG} and $10^4 \cdot$ AP(CaOx)index/[$Inh_{AGG} \cdot Inh_{GR}$] were positively correlated with CaOx-CR, with coefficients of correlation of 0.47 ($P = 0.003$) and 0.51 ($P = 0.001$), respectively.

A new formula was recently suggested by György and Ashby [14], in which the authors calculated the quotient between the sum of "solid" CaOx + "solid" CaP and the free citrate ion concentration, where solid refers to the ion-activity products of CaOx and CaP above the solubility product. It was assumed that the urine is in equilibrium with the two salts and that citrate is the major inhibitor of crystal aggregation. With this index the authors were able to classify 90% of 39 stone formers correctly with at least one of three samples. A normalization of this index by different therapeutic measurements was associated with freedom of recurrences during a follow-up of 36 months. Although this index appears to be a promising alternative and the authors claim that it has a high predictive power, no data were presented on its relationship to the severity of the disease.

Other important observations concerning the relationship between urinary findings and the clinical course of stone disease

Brundig et al. [6] calculated the thermodynamic risk of supersaturation in stone formers; they observed that the highest risk was during the night and concluded that analysis of oxalate, calcium, sulfate and potassium was sufficient for evaluation of the risk.

In a recent paper Daudon et al. [7] presented a crystallization risk index (CRI) derived in men from the excretion of calcium, oxalate, magnesium and potassium and in women from the excretion of calcium, oxalate, creatinine, magnesium and sodium. It is noteworthy that citrate was not a component in any of these indices. By relating the CRI value to the presence of calcium oxalate dihydrate crystalluria in morning urine the authors recorded sensitivity, specificity and predictive values that appeared to be comparable or superior to those obtained with the Parks and Coe index [26], Equil calculation of the supersaturation [49] and the AP(CaOx) index [38]. The predictive value of CRI in terms of recurrent stone formation has not so far been evaluated.

A stone formation risk index (SFRI) was proposed by Esen et al. [10]. The SFRI is based on the analysis of calcium, oxalate, uric acid, magnesium, citrate and urine volume in two 24-h urine samples. The authors found that 30% of first-time stone formers had a SFRI value

below 50, compared with 68% of recurrent stone formers.

In a large group of ESWL-treated patients Di Silverio et al. [8] carried out a multivariate analysis. They concluded that the age of the patient was inversely and urinary calcium, alkaline phosphatase and a history of previous episodes of recurrent stone formation were directly related to the occurrence of stone formation during a follow-up period of between 12 and 48 months (median 26 months). Although urinary phosphate, uric acid, sodium and magnesium were included in the analytical programme, these variables obviously had no predictive value. The authors made no attempt to summarize the different predictors in a common expression.

Comparison of the predictive power of some risk expressions

Clinical information on the course of stone disease following the 24-h biochemical evaluation was available for 754 men and 349 women. In these patients the following risk expressions were computed: AP(CaOx) index, AP(CaOx) $index_s$, calcium/citrate ratio, calcium/magnesium ratio, CaOx risk index ([calcium × oxalate]/[magnesium × citrate] and Parks and Coe scores. The levels of each of these expressions were compared between patients with and without recurrent stone formation during the follow-up period. Table 7 summarizes the percentage of patients with recurrent stone formation who had a value exceeding that recorded in 50% of the patients without recurrences. It is evident that the differences between the two groups in terms of these risk expressions were small and probably had no clinical importance.

It was recently shown [27] that the AP(CaOx) index was comparable with the crystalluria in morning urine, whereas the calcium/citrate-ratio and the Parks and Coe scores showed a more pronounced variation. Hopefully a better prediction of the further course of the disease can be obtained by combining the AP(CaOx) index with estimates of the inhibitory properties [45].

Table 7 Percentage of male and female patients with recurrent stone formation and a risk value exceeding that recorded in 50% of the patients without recurrences during the follow-up period

Risk formula	Men %	Women %
AP(CaOx) index	61	65
AP(CaOx) $index_s$	68	73
Calcium/magnesium	64	68
Calcium/citrate	73	69
$\frac{\text{Calcium} \times \text{Oxalate}}{\text{Magnesium} \times \text{Citrate}}$	69	70
Parks and Coe score	69	69

Conclusions

When urine composition is considered with respect to risk factors for CaOx stone formation, it is important to be aware of the variation that occurs during the day, between different days and between different periods of the year. Although the chance of identifying a specific abnormality and of drawing correct conclusions on the future course of the disease will probably increase with an increasing number of urine samples, in routine clinical work it is often necessary to limit the collection to a few urine samples, usually only one or two [39]. The majority of analytical results in the literature are derived from 24-h urine samples, as it is understood that urine formed during periods with a high risk will be diluted by urine formed during periods with a low risk.

Several of the risk formulas reviewed in this paper might be very useful in discriminating between stone formers and normal subjects. There is usually a considerable overlap between the two groups, however, and it should be pointed out that within the stone-forming population the identification of patients at particular risk of further stone formation is much more difficult. Although many authors have been able to demonstrate differences in urinary findings that could be related to the severity of the disease, others have not. There are probably several factors involved in this divergent outcome, but differences in patient selection, classification and follow-up might have contributed. Whereas in some patients changes in dietary, drinking and living habits might have affected urine composition to give a reduced risk of crystallization during the follow-up period, this will not be the case in others. It is obvious that the results also vary between different geographical areas, possibly because dietary differences, genetics and living habits influence the risk differently in different populations. For this reason it might be necessary to include population-specific risk factors in the formulas. It is also reasonable to assume that expressions containing many risk factors will be more informative than those with a few, but it is not possible from the present data to prove this.

Unfortunately there is as yet no risk formula based on findings in urine that provide a tool for an easy prediction of whether an individual patient will continue to form stones or not. Such an expression will probably not be in our hands until we fully understand all details of the process of stone formation. Until then we are restricted to expressions that only partly express the stone-forming propensity. Such expressions are helpful in therapeutic decision making only when considered in light of other clinical observations. Furthermore, in some expressions one or several risk factors might be overestimated, whereas in others the opposite might be case.

We have found that the 16-h daytime AP(CaOx) index and AP(CaOx) $index_s$ are higher in urine from stone formers than in urine from normal subjects [39, 45]

(unpublished observations) and presently prefer to use such a sample together with an 8-h night urine collection in the evaluation of stone formers [39]. Such an analytical programme gives us the opportunity of analysing pH as well as inhibitory properties in the night urine collected without any preservatives. My personal preference is to carry out only a limited biochemical analysis in first-time stone formers without a residual stone or fragments and to determine the risk of forming urine supersaturated with CaOx and CaP only in recurrent stone formers and in first-time stone formers with residual fragments or a residual stone. Special attention in the follow-up period is therefore paid to those with a high AP(CaOx) index, high AP(CaOx) $index_s$ or high AP (CaP) $index_s$. For patients with more severe disease, such as two or more episodes during a limited period of time, a complete evaluation including analysis of inhibitory properties is carried out to provide a basis for decisions on the therapeutic design.

Although as yet insufficient for reliable prediction of the further course of the disease, the risk formulas have a definite value in determining the type of advice that should be given once the therapeutic direction has been decided on, and they are extremely useful for judging the biochemical response to the treatment. We are, however, constantly searching for more efficient discriminators in urine that will enable even better prediction of the risk of stone formation.

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