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INVITED REVIEW

Metabolic risk-evaluation and prevention of recurrence in stone disease: does it make sense?

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Abstract In this review, aspects on the importance of information on urine composition and selection of the most appropriate regimen for prevention of recurrence are discussed. For patients with urolithiasis the treatment is facilitated by urine analysis with estimates of supersaturation levels. Despite lack of strong scientific evidence for the benefit of selective versus non-selective prevention of recurrence in patients with calcium stone disease, there is currently both convincing and logical information in support of tailored/selective treatment regimens aiming at correction of abnormal target variables. Such an approach is also recommended in the EAU and AUA guidelines. It is important, however, that every preventive regimen is balanced between the effects on urine composition and patients' tolerance to the treatment in order to achieve satisfactory compliance. It is possible that future improved understanding of the causes of calcium stone formation might provide a different therapeutic approach.

Keywords Calcium stones · Non-calcium stones · Stone analysis · Serum analysis · Urine analysis · Risk factors · Supersaturation · Prevention of recurrence · Dietary advice · Drinking advice · Pharmacological treatment · Selective treatment · Non-selective treatment

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Introduction

For the medical and metabolic care of patients with urolithiasis, there are two essential questions that immediately seek an answer. Is prevention of recurrence at all possible and of value and if so, does prevention of recurrence require metabolic risk-evaluation?

Before addressing this issue in detail, it is necessary to know that the risk of recurrent stone formation varies considerably between patients. It has accordingly been shown that without preventive treatment the recurrence risk for patients with cystinuria is around 85 % [1]. For infection and uric acid stone forming patients, despite lack of specific information, it can be assumed that the recurrence risk also is very high and probably at similar or even higher levels.

A more variable response to preventive treatment has been recorded and can be expected in patients who have formed stones composed of calcium salts; calcium oxalate and calcium phosphate. In these patients the average recurrence risk after 10 years is around 50 % [2, 3] (Fig. 1). Patients forming brushite stones (calcium hydrogen phosphate) have a particularly high recurrence risk as high as 70 % [3, 4]. But for the other calcium stone patients it stands to reason that while some will only form one stone during their life-time others are afflicted by a more severe disease with repeated stone formation and repeated need of active stone removing interventions. When patients, who had formed their first and only stone (S), were compared with those who had formed at least two stones (R) at the start of follow-up, two different courses were recorded (Fig. 1). For S-patients less than 30 % have formed one or several new stones after 10 years. This should be compared with a 10-year recurrence risk of almost 70 % for R-patients. It thus seems reasonable to assume that whereas

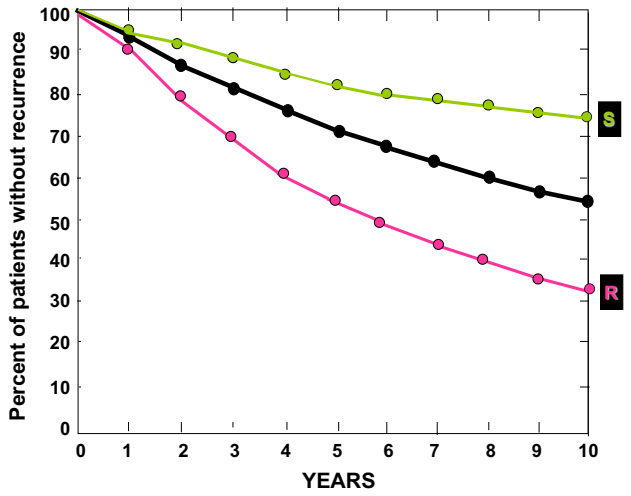

Fig. 1 Percentage of recurrence-free patients with calcium oxalate stone disease during a 10-year period. The *curve* was based on the assumption that that 55 % were first time stone former (S) and 45 % recurrent stone formers (R) [2] (permission granted by Karger AG)

R-patients might be motivated and in need of powerful prevention of recurrence, with few exceptions, S-patients are not. It also stands to reason that as long as no specific risk factors are demonstrated for the latter patients there is little need of long-term preventive efforts.

Which are the basic and absolutely necessary steps in evaluation of patients with stones?

Whichever history of stone formation the patient has presented, a quantitative stone analysis is mandatory [3, 5–7]. Without this information the future management of this large group of patients can only be based on indirect and insufficiently accurate assumptions. Although most analyses, for statistical reasons, will show that the stone is composed of calcium oxalate (CaOx) or mixtures of CaOx and some kind of calcium phosphate (CaP), it is when other stone constituents are demonstrated that the analytical efforts are richly rewarded.

For patients from whom stones or stone fragments have not been retrieved, indirect conclusions can be made from radiographic images (KUB, NCCT), from urine cultures, sodium nitroprusside tests (Brand's test) [8] and microscopic examination of urine sediments with or without pH-manipulation of the samples [9, 10].

Identification of brushite, cystine, uric acid and infection stones (magnesium ammonium phosphate, carbonate apatite, ammonium urate) as well as other rare stone components is of utmost importance for the future treatment strategy. Before starting treatment with the aim of preventing calcium stone formation, it is of course necessary to know that calcium stone formation really is the problem.

For every stone patient it is also, always, necessary to analyse some serum or plasma variables. Information on levels of calcium and phosphate as well as PTH, when necessary, is important for diagnosis or exclusion of hyperparathyroidism as the cause of stone formation. Moreover, the levels of creatinine as an estimate of the renal function and urate should be determined. Concentrations of sodium and potassium also advantageously might be included in the routine evaluation [3, 11, 12]. Preferably all these analyses should be carried out at the patient's first consultation. Later the opportunity to identify important abnormalities might have gone.

When is analysis of urine composition of value?

It is reasonably well recognized how non-calcium stones composed of struvite (magnesium ammonium phosphate/carbonate apatite), uric acid and cystine [13] form and how the prevention of recurrence should be designed. The treatment of these patients is, at least theoretically, fairly straightforward. For uric acid and cystine stones follow-up of the effect of treatment in terms of reduced supersaturation with the two salts is an extremely useful guide for adequate dosage of the pharmacological agents. The major problem in the prevention of recurrence, however, is encountered in patients with calcium stone disease. This is at least partly explained by our so far incomplete understanding of the precise mechanisms leading to calcium stone formation. Although considerable information has accumulated on factors contributing to CaOx stone formation [14–17], it is not possible to incriminate one single factor as being responsible for the pathological crystallization [18].

Is it necessary to carry out extensive analysis of urine composition in patients with calcium stone disease?

The primary goals of recurrence preventive treatment in calcium stone forming patients is to reduce supersaturation with respect to the relevant calcium crystal phase and, if possible, to increase the inhibitory properties of urine. Whereas the supersaturation can be assessed by approximate estimates of the corresponding ion-activity product (AP) [13] or probability index [19], it is much more difficult to measure the inhibitory activity in clinical routine workup [20] and sometimes difficult to make a correct interpretation of the relevance of the inhibitory measurements.

Table 1 Effects of dietary components on urine composition and risk of abnormal crystallization

Diet component	Biochemical effects	End result
Oxalate	Increased excretion of oxalate	AP_{CaOx} ↑ (fU)
Low calcium	Increased excretion of oxalate	AP_{CaOx} ↑ (fU)
High calcium	Increased excretion of calcium	AP_{CaOx} ↑ (fU)
		AP_{CaP} ↑ (fU)
		AP_{CaP} ↑ (nU)
Animal protein	Increased excretion of oxalate, calcium and urate. Deceased pH. Decreased excretion of citrate	AP_{CaOx} ↑ (fU)
		AP_{CaP} ↑ (nU)
		$AP_{uric\ acid}$ ↑ (fU)
Purine-rich food	Increased excretion of urate	$AP_{uric\ acid}$ ↑ (fU)
	Possibly increased CaOx precipitation?	
High phosphate	Increased excretion of phosphate	AP_{CaP} ↑ (fU)
		AP_{CaP} ↑ (nU)
Vitamin C	Increased excretion of oxalate	AP_{CaOx} ↑ (fU)
Vitamin D	Increased excretion of calcium	AP_{CaOx} ↑ (fU)
		AP_{CaP} ↑ (fU)
		AP_{CaP} ↑ (nU)
Sodium	Increased excretion of Na	AP_{CaOx} ↑ (fU)
	Increased excretion of calcium	AP_{CaP} ↑ (fU)
Coffee	Increased urine volume. Increased volume of nU?	AP_{CaP} ↓ (fU)
		AP_{CaP} ↓ (nU)
		AP_{CaOx} ↓ (fU)

fU Final urine, *nU* nephron urine, *AP* ion-activity product

Before addressing in detail the question above and deciding on the role of comprehensive risk-analysis, it is important to consider which tools are available for prevention of calcium stone recurrences. Table 1 lists the effects that different dietary constituents have on urine composition. This information is of value for giving appropriate dietary advice to the patients [21].

In addition to some general recommendations on dietary and drinking habits, there are also a number of pharmacological options that might counteract stone formation by correcting one or several urine abnormalities [22]. Some of the most commonly used or theoretically interesting pharmacological agents are summarized in Table 2. The list contains agents that now or previously have been used with the aim of counteracting calcium stone formation as well as some agents that might become important in future. The currently most interesting and most commonly prescribed pharmacological agents are thiazides (and indapamide), alkaline citrate and possibly allopurinol. Furthermore, calcium and magnesium supplements might be useful in patients with high intestinal oxalate absorption. In addition, probiotics such as *Oxalobacter formigenes* can be useful through the degradation of dietary oxalate. But the potential clinical usefulness of probiotics remains to be shown. Despite the fact that pharmacological preventive treatment has been an issue in focus for the management of patients with stone disease during decades, there are only few randomized controlled trials (RCTs). The information in the limited number of RCTs has recently been summarized in two reports [23]. The analyses resulted in some important conclusions on the relative risk of fluid intake, dietary habits and pharmacological treatment alternatives compared with that in placebo or control groups.

Should the individualized recurrence preventive treatment of patients with calcium stone disease be selective?

There are some fundamental requirements of the optimal prevention of recurrence. The treatment should eliminate or at least reduce the influence of abnormalities in urine composition. As a consequence, the preventive regimen should be effective and stop new formation of stones. Moreover, the treatment regimen must be well tolerated in order to enable high compliance.

One of the major arguments for the benefit of analysis of urine composition and identification of risk factors for calcium stone formation is that the findings should provide a basis for a selective or tailored treatment regimen. In view of the various possibilities to decrease the crystallization propensity, the fundamental question that has emerged is

Table 2 Pharmacological alternatives for correction of abnormalities of importance for abnormal crystallization of CaOx and CaP

Pharmacological agent	Biochemical effects	End result
Thiazide	Decreased excretion of calcium in urine. Increased uptake of calcium in the skeleton	AP_{CaOx} (fU) ↓
Indapamide		AP_{CaP} (fU) ↓
K-citrate	Increased urine pH and citrate	AP_{CaOx} (fU) ↓
NaK-citrate	Inhibition of CaOx and CaP growth and aggregation. Inhibition of CaP—induced precipitation of CaOx	Inh CaOx AGG
KMg-citrate		
Allopurinol	Decreased excretion of urate	$AP_{uric\ acid}$ (fU) ↓
	Possibly reduced precipitation of CaOx?	
Calcium supplement	Decreased intestinal absorption and excretion of oxalate in patients with enteric hyperoxaluria. Decreased excretion of oxalate in case of insufficient intake of calcium	AP_{CaOx} (fU) ↓ Correction of negative calcium balance
Furosemide	Dilution of nephron urine at levels below the thick ascending loop of Henle	AP_{CaP} (nU) ↓
	Increased excretion of calcium	
Magnesium supplement	Increased urine magnesium. Favourable effect on Ca/Mg and on brushite precipitation. Inhibition of CaP growth	AP_{CaOx} (fU) (↓) Substitution of Mg-losses during Tz treatment
Orthophosphate	Decreased excretion of calcium. Increased excretion of PP	AP_{CaOx} (fU) (↓) Inh. CaOx GR Inh. CaP GR
Bisphosphonate	Decreased excretion of calcium	AP_{CaOx} (fU) ↓ AP_{CaP} (fU) ↓
Pyridoxine	Decreased excretion of oxalate in patients with primary hyperoxaluria type I	AP_{CaOx} (fU) ↓
Fluid intake	Dilution of fU and nU	AP_{CaOx} (fU) ↓ AP_{CaP} (fU) ↓ AP_{CaP} (nU) ↓ $AP_{cystine}$ ↓ APuric acid ↓
Probiotics	Re-colonization of the intestine with *Oxalobacter formigenes*	AP_{CaOx} (fU) ↓
	Decreased oxalate absorption	

nU nephron urine, *fU* final urine, *GR* crystal growth, *AGG* crystal aggregation

if selective/tailored recurrence preventive treatment based on urinary findings is better than treatment with any of the alternatives listed in Tables 1 and 2, irrespective of information on urinary risk factors and thus without the need for metabolic workup.

Unfortunately the literature is a poor guide in that regard. There is so far only one RCT carried out in first time stone formers that demonstrated a significantly better outcome in patients given tailored dietary recommendations according to urine composition than in patients who only were given empirical advice without biochemical support [24]. Otherwise, there is indeed weak evidence in favour of selective rather than non-selective preventive treatment. None of the available RCTs or other comparative studies provide strong scientific basis for definite recommendations on which therapeutic regimen to choose. It therefore is necessary to look in more detail on how different authors have used the various treatment options.

When scrutinizing available publications, it is obvious that a selective treatment approach has been applied in most of them [3, 23, 25]. Very few studies on patients treated in a non-selective way have had the results analysed according to the biochemical profile of urine. In those few cases in which this matter has been touched, the follow-up periods have been short, and in most reports results after more than 3 years of treatment are exceptional [26–29].

In careful reviews of RCTs [30, 31] the general impression was that most studies had a low level of evidence. Moreover, it is of note that many of these studies were carried out several years ago, as shown for pharmacological

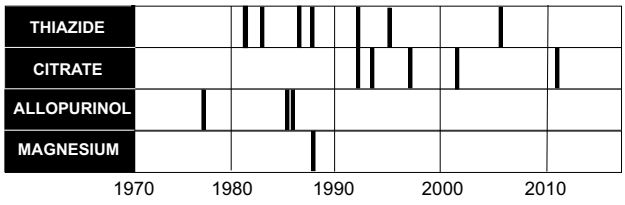

Fig. 2 Publication times for RCT studies on pharmacological treatment [30, 43]

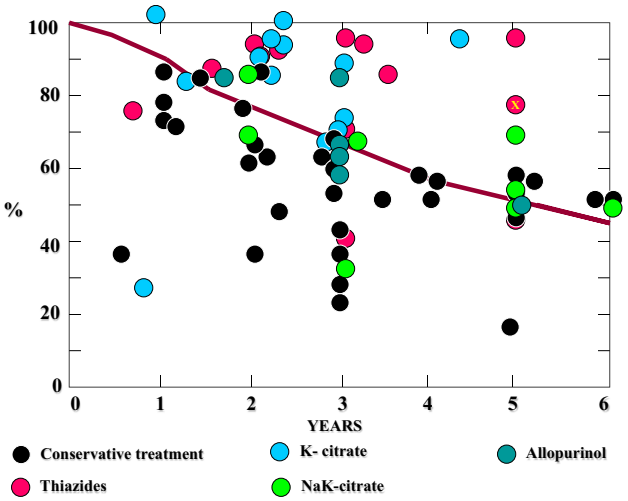

Fig. 3 Percent of patients without recurrent stone formation in pharmacologically and conservatively treated calcium stone disease (summary of literature data)

treatment in Fig. 2. There is a striking lack of recent publications on prevention of recurrent stone formation. This is in sharp contrast to the almost unlimited number of studies on α-receptor antagonists that have generated almost an avalanche of comparative studies, RCTs and meta-analyses of effects that we already know enough about. But a closer analysis of the results of long-term stone preventive treatment obviously has not attracted urologists in the same way.

In RCT studies significantly reduced risk of stone formation was recorded during treatment with thiazides, alkaline citrate (potassium citrate, sodium potassium citrate and sodium magnesium citrate) and also to some extent allopurinol [30–32]. A proper understanding of the relative role of the most commonly used pharmacological agents is, however, difficult to discern and in some regards the reported findings were surprising. It is obvious, however, that with appropriate recurrence preventive treatment, the course of the disease can be favourably affected. This has been demonstrated in numerous publications as shown in Fig. 3 and it has also been shown that rational prevention of recurrent stone formation is cost effective [33].

Thiazide was primarily used because of its calcium reducing effect [34]. Accordingly treatment with thiazide was initially as well as subsequently preferably prescribed to patients with hypercalciuria, but it was earlier suggested by Yendt and co-workers that this agent was clinically effective also in normocalciuric patients [35]. The conclusion was that this treatment could be given to patients irrespective of urine composition. Whether there are any differences in effects on prevention of recurrence between thiazide-treated patients with and without high urinary calcium has very seldom been analysed in long-term RTCs or other comparative studies.

Ala-Opas [36] showed significantly reduced excretion of calcium in patients intermittently treated with thiazide. During a 2-year follow-up period 86 % of the hypercalciuric patients were without recurrent stone formation compared with only 71 % in the normocalciuric group. But these patients were also given bran, low-calcium and low-oxalate diet and the treatment period was too short for adequate conclusions. In numerous other studies on patients treated with thiazides in a selective or non-selective way no obvious differences in the effects on prevention of recurrence were recorded. Unfortunately, in most studies of patients treated in a non-selective way, the fraction of normocalciuric patients is unknown and conclusions on whether selective treatment is better than non-selective cannot be drawn.

Although thiazides, alkaline citrate and allopurinol are assumed to have completely different mechanisms for correcting specific target risk factors, it is really surprising that when the clinical outcome was compared between patients treated with thiazide + potassium citrate and thiazide + allopurinol [30], no differences were recorded compared with treatment results in those patients who only were given thiazide. For thiazide + potassium citrate given non-selectively the relative risk for the combined treatment was 0.94 and recurrent stone formation seen in 30 and 32 % of the patients [30]. When the effect of the combination thiazide + allopurinol was compared with that in those patients who were given only thiazide, the relative risk was 0.79 and recurrent stone formation recorded in 13 and 16 %, respectively [30]. Much better prevention of recurrence would have been expected with the combined approaches, but that was thus not the case. These findings might indicate that thiazide has a more general effect than the other agents, but without details on urine composition in the treated patients such a conclusion cannot be drawn.

It is generally recommended that potassium citrate should be given to patients with hypocitraturia or in cases of low urine pH. In most studies with alkaline citrate the patients also had a low excretion of citrate. Alkaline citrate, in addition to its citrate increasing effect, favourably increases urine pH as well as inhibition of crystal growth

and aggregation. It is thus theoretically possible that alkaline citrate might have a more general indication than is the case for thiazide. There are, however, no RCTs supporting this conclusion.

For allopurinol our own experience based on the results in 99 patients treated with 300 mg/day during a period up to 8 years, irrespective of urine composition [37], recurrent stone formation was recorded in 57 % of those who followed the regimen during more than 5 years. This recurrence rate was about the same as that reported from several other studies of untreated calcium oxalate stone forming patients. The side effects of allopurinol in that study were insignificant, but so was also the preventive treatment effect. Allopurinol might be of value for patients with calcium oxalate stone formation and simultaneous hyperuricosuria and the conclusion from literature data is that the requirement for choosing allopurinol should be hyperuricosuria, but there are no recent publications supporting that conclusion.

Side effects of these agents vary considerably from one report to another. Literature data showed side-effects between 0 and 59 % for thiazides [30]. In our own thiazide-treated patients as many as 31 % stopped the treatment because of uncomfortable side-effects [38]. Although the frequency of side-effects recorded in patients treated with alkaline citrate were between 7 and 42 % these problems were usually milder than those observed with thiazides. Side effects reported for allopurinol were in a range of 0–37 % [30].

It seems reasonable to assume from what has been stated so far that the most appropriate selection of medical treatment should be directed towards those abnormal urine variables that might have the most powerful effect on the demonstrated abnormalities. This means for instance that in case of hypercalciuria thiazide is the treatment of choice. In case of hypocitraturia treatment with alkaline citrate should be the natural treatment. Each one of the other therapeutic options also should be chosen according to the predicable effect on urine composition. In the clinical routine it is necessary, however, always to find a balance between the most pronounced effect on urine composition and the tolerance of the regimen in order to get the long-term compliance. Without successful patient compliance every kind of preventive treatment will fail.

The interpretation of literature data has resulted in recommendations in the EAU and AUA guidelines [39] of an essentially selective dietary and pharmacological approach. In conclusion, hypercalciuria accordingly should be the preferred indication for treatment with thiazides/indapamide. For the same logical reason hypocitraturia with or without low urine pH is the natural indication for alkaline citrate. With identical arguments it does not make sense to recommend specific dietary restriction of oxalate to patients with a normal or low urinary oxalate. Neither can it be advisable to recommended reduced intake of animal protein to those who have a normal calculated protein intake. It thus stands to reason that the best benefit from any specific dietary or pharmacological treatment requires identification of abnormal corresponding target variables. This information cannot be obtained without appropriate urinary risk-factor analysis.

The outcome of long-term selective recurrence preventive treatment is perhaps best supported and exemplified by the data published by Parks and Coe. They recorded a significant reduction in stone recurrences in patients treated for up to 20 years [40]!

For which calcium stone patients should preventive treatment be considered?

Based on the findings, assumptions and recommendations summarized above it stands to reason that analysis of urine composition to identify risk factors should be a natural part of the workup and a basis for further therapeutic conclusions in patients with severe recurrent calcium stone disease [11, 25].

Patients with severe stone disease (Rs) constitute a group that is attributable to clinical characteristics almost always will qualify for pharmacological prevention of recurrence [11, 25]. For patients with a mild recurrent disease (Rm) general conservative measures might be sufficient. But what do we mean by severe recurrent stone former? To identify this patient information on the previous history of stone formation is essential. In the literature, the frequency of stone formation is often used as an estimate. This is a measure that is difficult to calculate and difficult to use appropriately [41]. My own routine therefore has been to calculate stone age index (SAI) from the total number of stones formed relative to the age of the patient (100 $\times$ total number of stones/patient's age) [11, 42]. A value $\geq$10 clearly indicates that the patient has a disease that deserves attention. Other risk factors, that also need to be observed and that qualify the patient for being referred to the Rs-group, are: early start of stone formation (age <25 years), family history of stone disease, brushite-stone, as well as disease(s), pharmacological treatment and anatomical risk factors known to be associated with stone formation.

Currently the problem has been complicated by the presence of residual fragments after stone removal. In the literature, residual fragments are presented as more or less synonymous with the situation after SWL. Although fragments are more common in that group of patients, it is important to be aware of the fact that residual fragments also are encountered in patients treated with PNL, URS and RIRS. Also patients with residual stones or

fragments should be considered for active prevention of recurrence even if they only can be categorized as Rm or even S-patients. It was previously demonstrated that the recurrence rate was higher in patients who had high SAI and high AP(CaOx) than in those with low SAI and low AP(CaOx) (Fig. 4) [42]. It thus can be recommended to consider preventive treatment for all calcium oxalate stone patients with residual fragments, high AP(CaOx) and high SAI.

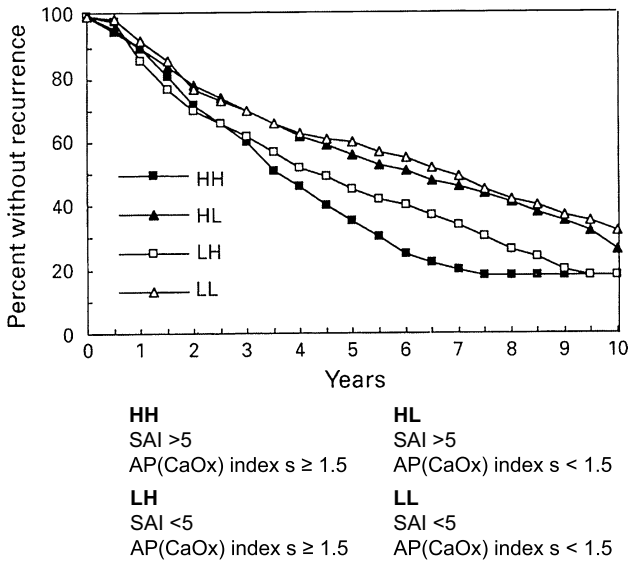

Fig. 4 Course of stone disease in patients with different combinations of SAI and AP (CaOx) index s [42] (permission granted by Karger AG)

Analysis of urinary risk factors for calcium stone formation

Based on the conclusions summarized above and the recommendations that prevention of recurrence in calcium stone disease should be as selective as possible, identification of risk factors is mandatory.

Historically urine has been and still is collected during one or several 24-h periods [12] or occasionally during some other long-term collection period [11]. From a relatively extensive analysis of urine variables it is possible to use the major determinants of ion-activity products of CaOx and CaP to derive approximate estimates of the ion-activity products of these two stone constituents. In addition, the urine analysis shown here also gives information on supersaturation with uric acid (Fig. 5). It needs to be emphasized, however, that for measurements of urate and pH another preservative than hydrochloric acid or boric acid is necessary.

When estimates of the ion-activity product of CaOx were adjusted for a standardized 24-h urine volume of 1500 mL (AP/CaOx) index s [43], it was shown that the risk of stone formation was significantly greater in patients with high values of AP(CaOx) index s than in those with low indices (Fig. 6) [42]. By comparing ion-activity products and formation products [13], it is possible to calculate which average urine volume that is necessary for avoiding pathological crystal formation.

When the urine has been completely analysed it is thus possible to identify the factors of greatest relevance for abnormal levels of supersaturation. We can accordingly

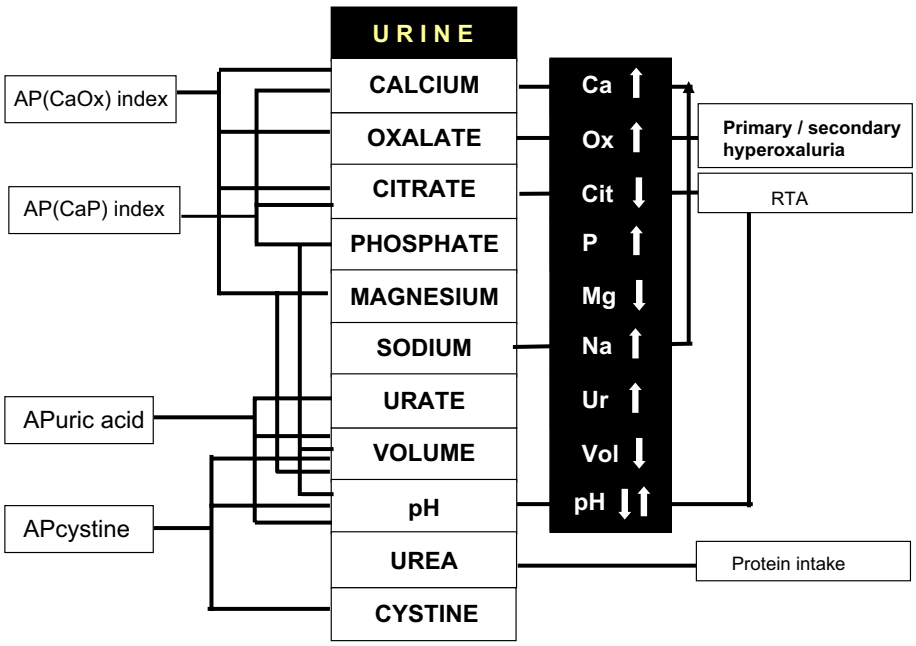

Fig. 5 Urine variables included in the risk analysis from which approximate estimates of ion-activity products of calcium oxalate, calcium phosphate, uric acid and cystine can be calculated. Information on abnormal target variables provides the basis for a tailored/selective treatment. Moreover, the analytical data indicate if the patient has primary/secondary hyperoxaluria or renal tubular acidosis

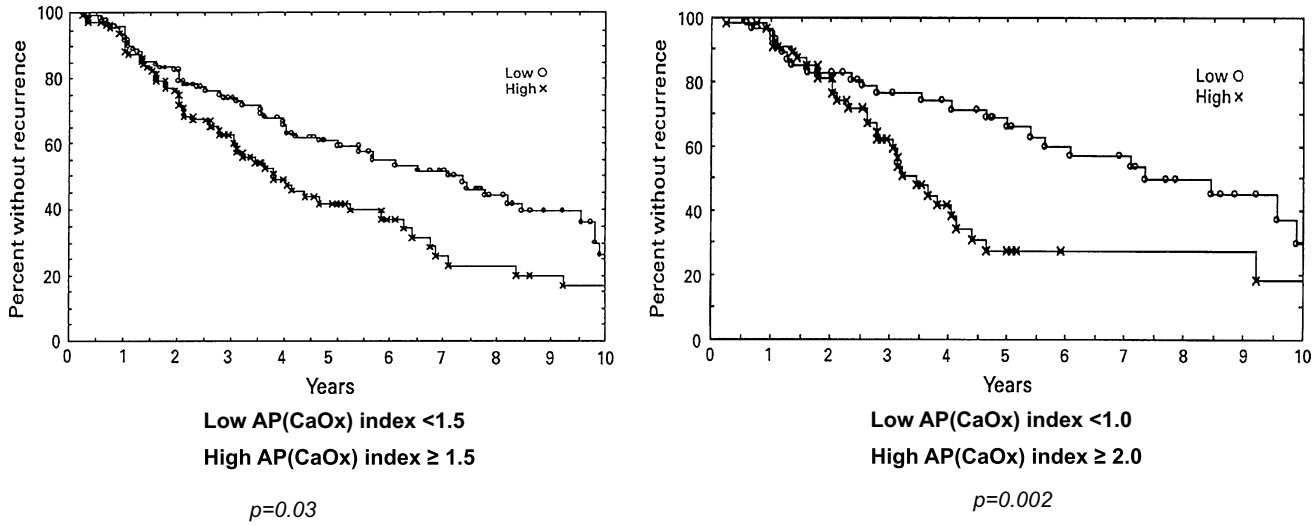

Fig. 6 Course of stone disease in patients with different levels of AP(CaOx) index s [42] (permission granted by Karger AG)

Table 3 Summary of conclusions that can be made following analysis of urine composition in comparison with absence of this kind of information

Conclusion of importance for decisions regarding prevention of recurrence	With urine analysis	Without urine analysis
Diagnosis of primary hyperoxaluria	Yes	No
Diagnosis of secondary hyperoxaluria	Yes	No
Identification of patients with RTA	Yes	No
Calculation of necessary urine volume	Yes	No
Information on supersaturation levels	Yes	No
Hypercalciuria	Yes	No
Hypocitraturia low or high pH	Yes	No
Hyperuricosuria	Yes	No
Demonstration of excessive protein intake	Yes	No
Basis for tailored dietary advice	Yes	No
Arguments for patient information	Yes	No

conclude on the level of urine flow, hypercalciuria, moderate hyperoxaluria, hypocitraturia, hypomagnesuria, hyperphosphaturia, hyperuricosuria, and high or low urine pH. This information is thus fundamental for selective or tailored recurrence preventive treatment.

In this regard it also needs to be mentioned that the urine analysis might enable diagnosis of some specific diseases that are associated with stone formation, such as primary and secondary hyperoxaluria [44], complete or partial renal tubular acidosis [12], the possible negative effects of treatment with acetazolamide [45], excessive intake of sodium [46] and animal protein [11, 44].

Table 3 shows what we can get with and without analysis of urine composition in patients with severe calcium stone disease.

By showing and discussing the urinary findings with the patients it is at least to some extent possible to reply to his or her questions and also to show why a specific treatment has been recommended. This is an extremely important pre-requisite for successful long-term compliance.

Another important aspect is that follow-up analysis of urine composition should be carried out at regular intervals in order to record the biochemical effects of the treatment. This step is necessary to confirm compliance and to show the patient that the therapeutic efforts at least have resulted in the anticipated effect on urine composition. Prevention of recurrence in patients with stone disease is nothing that is finished once the metabolic evaluation has been completed and choice of preventive treatment has been made. For patients with severe stone formation, it is, both for the patient and for the urologist, a long-term undertaking without which compliance will be low and the preventive effect weak or non-existent.

Other information of importance for the decision on recurrence preventive treatment

Before finally deciding on how the long-term recurrence preventive regimen should be designed it is essential to take a brief dietary history [39, 47]. A comprehensive dietary

history is a difficult and complicated procedure that certainly best is carried out by a dietician, but in the absence of such assistance there are some relevant questions that need an answer:

- Is the calcium intake extremely low or extremely high?
- Is there an over-consumption of food stuffs rich in oxalate?
- Does the patient take supplements of vitamin C or D?
- Is there a frequent and high intake of animal protein?
- How are fluid losses compensated?

It is also very helpful with some questions on the patient's life-style [16]:

- Is the patient regularly active with sport and/or training?
- Is sauna-bath part of life?
- Are visits in tropical areas common?

Conclusion

The conclusion from these observations is that tailored dietary as well as pharmacological treatment should be the preferred way to go. This is thus a logical consequence of how our understanding of stone formation should be used in order to decease or arrest stone formation.

Such a strategy can also be found in both EAU and AUA guidelines [3, 39]. This means that identification of risk factors and patterns of abnormal urine composition should provide the natural basis for individually designed prevention of recurrence in patients with severe disease (Rs) and pronounced risk of future stone problems.

Despite lack of solid scientific evidence, the recommendation to choose a selective preventive treatment with the aim of correcting abnormal urinary target risk variables is likely to be superior to a non-selective approach. This treatment strategy that should be reserved for patients with severe disease requires an adequate analysis of urinary risk factors.

Although an effect can be anticipated with several therapeutic alternatives, the selection should be made with optimal compliance and minimal side effects in view. It is possible that increased understanding of the details of calcium stone formation, as well as access to improved treatment alternatives, might provide a different future interpretation of the literature and different therapeutic principles.

Compliance with ethical standards

Conflict of interest The author has no conflict of interest.

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