Urol Res (1998) 26:77–81

INVITED EDITORIAL

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Stone prevention: why so little progress*?

Received: 5 June 1997 / Accepted: 13 August 1997

Abstract Despite intensive research the knowledge of stone pathogenesis, which is the basis of every rational stone metaphylaxis, has remained rather scanty. Epidemiology shows that stone formation in most patients is only a sporadic event, probably resulting from a coincidence of different factors. The hypercalciuria, hypocitraturia, hyperuricosuria and hyperoxaluria frequently found in calcium stone formers can be influenced therapeutically and, in affluent societies, seem to be the result of protein over-consumption. These four factors favour crystallization processes in urine. However, urine is normally protected from nucleation, growth and aggregation of calcium minerals by crystallization inhibitors. In urine, crystallization of calcium oxalate can only be induced by an extreme supersaturation, a deficient inhibitor activity and promoters of crystallization. To form a stone, crystals have to be retained in the urinary collecting system. Two mechanisms of retention are discussed: large crystal aggregates trapped in collecting ducts of renal papillae, or a pre-existing calcification of the papilla (mainly calcium phosphate) that may be responsible for growth of an initially fixed particle to a concretion large enough to become symptomatic. An excessive oxalate intake combined with a low calcium consumption can produce marked hyperoxaluria. In the animal model, hyperoxaluria induces not only calcium oxalate crystallization but also papillary damage and incrustrations. Hypercalciuria at a low pH favours the aggregation of calcium oxalate, and at a high pH the crystallization of calcium phosphate, a promoter of heterogeneous nucleation of calcium oxalate. All these factors and further complex phenomena mentioned in this paper have to be taken in account to perform rational stone metaphylaxis.

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* This paper is dedicated to Professor G. Rutishauser, Basel, who has promoted stone research for more than 30 years.

Key words Urolithiasis · Stone metaphylaxis · Urinary crystallization processes

Introduction

As everywhere in science, an increasing gap between technology and basic research can be observed in urolithiasis research. While "stone machines" and sophisticated percutaneous and endourological techniques have revolutionized stone treatment, the knowledge of stone pathogenesis, fundamental for a rational stone metaphylaxis, has remained rather scanty. Opinions about the efficiency of calcium stone metaphylaxis by thiazides and potassium citrate are controversial [12, 24]. Whether dietary calcium restriction still has a place in stone metaphylaxis [11] or whether a high dietary calcium intake even decreases the risk of symptomatic stone disease [15] is a matter of debate. Many urologists have lost interest in stone prevention and the pharmaceutical industry has cancelled sponsorship of stone research. However, the incidence of urolithiasis in the population of Western countries exceeds 10% [46], and in long-term surveys a recurrence rate of at least 60–75% was reported [3, 51]. In the United States the total annual costs of urolithiasis were recently estimated to be $1.83 billion [14]. Therefore the editorial board of this journal has initiated a paper which should "stress the difficulties of stone research" and elucidate "major points of interest and expected future development".

This paper is restricted mainly to calcium oxalate nephrolithiasis, which not only is the most frequent but also, from a pathogenetic and metaphylactic point of view, the most problematic stone disease.

What can we learn from epidemiology?

Although stone incidence and recurrence rate are high in Western populations, in most individuals stone episodes occur only occasionally. In one of the most extensive

retrospective studies (538 patients followed for an average of 18.5 years) the average time interval between the initial stone event and the first recurrence was 9.5 years, and only 26% of the patients had more than two recurrences [51]. In more recent studies, the recurrence rate was 24% or 26% respectively during a 10-year follow-up [3, 10]. The active recurrent stone formers (at least one stone episode annually) usually examined in stone trials are found in about 6% of the stone population [25, 51].

Another phenomenon complicating metaphylactic studies is that most stones seem to form during a limited span of life [16]. Stone formation seems to fade out with time [25]. Therefore the question arises whether stone metaphylaxis should be studied in age-matched rather than randomized patients.

Stone epidemiology shows that stone formation in the upper urinary tract is increasing in all affluent societies [4]. Socio-economic studies revealed that this phenomenon may be related to an increased consumption of animal protein [39]. High protein intake is known to produce hypercalciuria, hypocitraturia, hyperoxaluria and hyperuricosuria, the four urinary alterations frequently found in stone disease [20]. Therefore the question arises as to whether stone formation is a metabolic disease.

Is stone formation a metabolic disease?

For a long time, calcium urolithiasis has been connected with hypercalciuria and dietary calcium restriction was the treatment of choice. Much effort was expended to find out whether hypercalciuria was the result of increased intestinal calcium absorption, increased bone resorption or a renal calcium leak. Some authors even distinguish seven different types of hypercalciuria and recommend selective treatment with calcium restriction, thiazides, orthophosphate, sodium cellulose phosphate or indomethacin [11]. In their highly selected groups of patients, these authors reported very successful treatment by these measures. However, in some other studies with less selected patients, such beneficial effects could not be confirmed [12, 25].

Studies comparing rates of stone episodes and urinary composition showed a strong correlation between the severity of stone disease and urinary oxalate but not urinary calcium excretion [38]. Such findings and the improved methods for analysing oxalate have turned the interest of stone research to urinary oxalate. With low oxalate consumption, oxalate excretion is mainly of metabolic origin. Recently a genetic control of oxaluria by a pair of co-dominant alleles for high and low renal excretion was postulated [27]. In this genetic study relative hyperoxaluria was found in 9% of 101 controls and 28% of 101 stone patients. Also, in the 24-h urine of 3473 calcium stone formers examined under free diet in five different regions of the USA, moderate hyperoxaluria was found with a frequency of only 18–25% [20]. Under an identical diet, oxaluria was equally present in 23 recurrent calcium stone formers and 16 healthy controls without any case of hyperoxaluria in either group [8]. However, after an excessive dietary oxalate load of 1200 mg, oxaluria increased in both groups by at least 300%. Diet-induced hyperoxaluria was abolished when the oxalate load was combined with a high calcium consumption at the same meal [2]. This finding may explain why in a recent prospective study of about 46 000 men a high dietary calcium intake diminished the risk for the development of kidney stones by about 40% [15]. This latter study, together with the finding of a decreased bone density in hypercalciuric stone patients [18, 29], has resulted in some consternation among stone patients and their doctors. However, it has to be pointed out that the abovementioned study was originally designed to follow vascular disease and cancer and is not representative for stone formers, because 8.7% of patients with a previous history of kidney stones as well as the age group below 40 years (that is often affected by stone formation) were excluded.

As we will show below, metabolic disorders, although important for urolithiasis, are rarely the single cause of stone formation.

Can stone formation be explained by crystallization processes in urine?

It has been generally accepted that stone formation is a crystallization process in urine supersaturated with stone minerals and that this supersaturation is the driving force for the formation of a crystal nidus (nucleation) and its transformation into a visible particle (crystal growth).

The state of urinary supersaturation can be measured by comparing the concentration product (e.g. calcium × oxalate) before and after equilibrating urine with the corresponding stone mineral (e.g. calcium oxalate) and expressing the state of saturation as the corresponding concentration product ratio (CPR) [35]. The main objections to this method are the difficulty of obtaining an equilibration in the presence of inhibitors and the dependency of the results on the crystal density used for the equilibration [22]. Supersaturation is most often expressed as relative saturation (RS). RS is the ratio between the activity product of the stone-forming ions in urine and the corresponding solubility product obtained from artificial solutions. Activity products are calculated using special software [13]. This computer program is based on the chemical analyses of 15 to 23 urinary compounds and the calculation of more than 100 complexes formed between these solutes. Apart from the extensive chemical analyses the main drawback of this method is that it neglects the effect of urinary macromolecules. Activity products can be estimated by the calculation of activity product indices from five urinary parameters using empirical formulas [48]. The state of saturation can also be expressed by the difference (s) between the concentration of a substance in

solution and the solubility of the substance [44]. Recently we have developed a simple method to determine this difference with respect to calcium oxalate in native urine [6].

Average values for CPR, RS and s calculated for normal urine and for urine with a high calcium and oxalate concentration respectively, are shown in Table 1. The table demonstrates that an increase in calcium and oxalate had almost an identical influence on CPR whereas s was almost exclusively dependent on urinary oxalate. Such a predominant influence of oxalate was also found when correlating urinary oxalate with the rate of stone episodes [38], the extent of crystalluria [38] and the state of urinary saturation with calcium oxalate in equilibration experiments [2]. The use of the difference between the solute and the solubility allows an exact description of nucleation and growth of calcium oxalate in native urine by a simple equation [6].

Since even in healthy subjects urine is often supersaturated with calcium oxalate (CPR and RS above 1.0 and s positive in Table 1), the main question is not why stones form but why stones do not form more often [17]. The presence of important crystallization inhibitors in urine is a 40-year-old answer to this question [28]. Low molecular weight inhibitors such as citrate and macromolecular substances such as glycosaminoglycans, Tamm Horsfall protein (THP), osteopontin, nephrocalcin, uronic acid-rich protein and urinary prothrombin fragment 1 [41, 42] have a high affinity for calcium ions. By their ability to adsorb to crystal surfaces and nidus, some inhibitors can block nucleation, growth and aggregation even in nanomolecular concentration. Abnormal THP [23] and nephrocalcin [34] levels have been found in stone formers. Although abundant test systems have been developed to study crystallization processes [22, 30] a general lack of inhibitor activity often postulated in urine of stone formers could not be proved until now. A major problem is that most tests were performed in well-controlled artificial solutions with the addition of only a few per cent of urine. However, results obtained with diluted urine are only of limited clinical value, since urinary crystallization properties can change markedly with urinary dilution [37]. Even centrifugation and filtration of urine, which removes important macromolecules, influences test results [43].

Measuring the critical oxalate concentration necessary to induce crystallization in native urine revealed extreme values, rarely observed in urine [5]. This is in agreement with the fact that calcium oxalate crystals are only rarely present in urine examined immediately after voiding and without cooling [21, 47]. However, the critical supersaturation to induce crystallization is reduced by the action of promoters presenting preformed surfaces to the solution [5, 41]. Polymerized Tamm Horsfall protein and membranous cellular degradation products are such promoters, but their importance for stone formation has not been clarified [41]. Also heterogeneous nucleation of calcium oxalate by calcium phosphate is still under debate [7, 26]. Hypercalciuria and a high urinary pH are the two factors mainly responsible for urinary supersaturation with calcium phosphate [2].

Urinary stones consist of crystal aggregates embedded in a macromolecular matrix [1]. The question whether stone formation is a process of crystallization and secondary adsorption of urinary macromolecules [50] or the mineralization of a preformed matrix [1] remains open. The finding that even the smallest crystals in urine are coated by urinary macromolecules [31] suggests that crystal and matrix formation are simultaneous rather than consecutive processes. The question whether this coating inhibits or promotes stone mineralization has not been answered definitively [42].

Table 1 Values of various parameters in normal urine, high-calcium urine and high-oxalate urine. *CRP* concentration product ratio (Ca × Ox before/Ca × Ox after equilibration with calcium oxalate), *RS* relative saturation (activity (*a*) product [*a*Ca × *a*Ox]/thermodynamic solubility product obtained in artificial solutions), *s* calcium oxalate concentration, which to reach saturation can be precipitated from supersaturated or dissolved in undersaturated urine.

	Normal urine	High-calcium urine	High-oxalate urine
Ca (mmol/l)[a]	2.52	8.18	2.51
Oxalate (mmol/l)[a]	0.22	0.22	0.78
CRP[a]	2.18	9.30	10.73
RS[a]	5.78	11.77	19.30
s (mmol/l)[b]	0.11	0.20	0.68

[a] Data from [35]
[b] Calculated from these data by:

$$s = \frac{(Ca + Ox) - \sqrt{(Ca + Ox)^2 - 4CaOx(1 - CRP^{-1})}}{2}$$

The problem of crystal and stone retention

Crystalluria and stone formation are far from synonymous. Crystalluria can be considered a useful process to manage a dangerous episode of urinary supersaturation by forming a large number of small crystals that are rapidly washed out of the urinary tract. For the formation of a clinically symptomatic stone, crystals have to be retained.

About 30 years ago it was already recognized that aggregation may be the most important process for stone formation [40]. But a method allowing the direct measurement of this phenomenon in supersaturated solutions such as urine has yet to be developed. Recently, in a computer model, it was calculated that at high supersaturation calcium oxalate aggregates may become large enough to be trapped in the ducts of Bellini and thus to give rise to growth of initially fixed particles into a stone [33]. However, even in concentrated overnight urine that was examined after an oral oxalate load, large aggregates were found only rarely [9]. Apart from citrate, urinary macromolecules seem to be

the most important inhibitors of aggregation [41]. Tamm Horsfall protein can change from an inhibitor to a promoter of aggregation by polymerization [23]. This polymerization is favoured by a highly concentrated urine, a high urinary calcium and a low pH. Concentrated urine, hypercalciuria and hypocitraturia with a low urinary pH are frequent findings in calcium stone formers [20].

Recently much attention has been paid to crystal-cell interaction in renal tubules [49]. In animal models it has been shown that calcium oxalate crystalluria caused renal epithelial injuries with loss of epithelium, exposure of basement membranes to urine and incrustration of renal papillae [32]. Membranous cellular degradation products always found in urinary crystals and stones proved to be excellent nucleators of calcium oxalate [31]. The calcium phosphate incrustrations frequently found in urinary stones and renal papillae (Randall's plaques) were also claimed some time ago to be responsible for nephrolithiasis [36]. However, renal medullary calcification was found in all of 100 randomly selected autopsies [19].

Conclusions

Epidemiology shows that stone formation in most patients is a sporadic event and probably the result of an accidental coincidence of different unfavourable factors. In urolithiasis research too often only individual factors have been studied. Future stone research should preferably try to elucidate and measure critical constellations initiating stone formation. In view of the generally sporadic nature of stone events and the new facilities for stone removal, metaphylaxis in most cases can be limited to a high fluid intake and a moderate protein intake without dietary calcium restrictions. All dietary excesses, especially those with oxalate, should be avoided. Reliable stone analyses by infrared spectroscopy and X-ray difraction analyses are still mandatory. Stone-associated diseases such as urease-positive infection, gout, hyperparathyroidism, renal tubular acidosis and morphological anomalies of the urinary tract have to be kept in mind. In most cases they can easily be excluded by simple urine and serum analyses or by the radiological examinations necessary for stone diagnosis. The few stone patients with short-term recurrence may benefit from more extensive investigations and from specific treatment [45].

References

1. Achilles W, Khan SR (1995) The matrix for in vivo crystal initiation. In: Rao PN, Kavanagh JP, Tiselius HG (eds) Urolithiasis: consensus and controversies. South Manchester University Hospitals, Manchester, pp 5–11
2. Ackermann D, Baumann JM (1987) Chemical factors governing the state of saturation towards brushite and whewellite in urine of calcium stone formers. Urol Res 15:63–65
3. Ahlstrand C, Tiselius HG (1990) Recurrences during a 10-year follow-up after first renal stone episode. Urol Res 18:397–399
4. Andersen DA (1969) Historical and geographical differences in the pattern of incidence of urinary stones considered in relation to possible aetiological factors. In: Hodkinsons A, Nordin BEC (eds) Renal stone research symposium. Churchill, London, pp 7–31
5. Baumann JM, Affolter B, Brenneisen J, Siegrist HP (1997) Measurement of metastability, growth and aggregation of calcium oxalate in native urine: a new approach for clinical and experimental stone research. Urol Int (in press)
6. Baumann JM, Affolter B, Siegrist HP (1997) Measurement of metastability and growth of calcium oxalate in native urine by calcium electrode: a new approach for clinical and experimental stone research. Scanning Microsc (in press)
7. Baumann JM (1990) Physico-chemical aspects of calcium stone formation. Urol Res 18 [Suppl 1]:25–30
8. Baumann JM, Lauber K, Lustenberger FX, Wacker M, Zingg EJ (1985) Crystallization conditions in urine of patients with idiopathic recurrent calcium nephrolithiasis and with hyperparathyroidism. Urol Res 13:169–174
9. Baumann JM, Futterlieb A, Lustenberger FX, Wacker M (1984) Kristallisationsphänomene im Harn nach alimentärer Oxalatbelastung. Fortschr Urol Nephrol 22:151–155
10. Boulahrouz R, Ang KS, Mignard JP, Carlier M, Trifard F, Cloup C, Corbel L, Ratajzack A, Cam G, Charasse C, Le Cacheux Pr, Simon P (1997) A prospective survey of the incidence of urolithiasis in a French region during the last decade (1985–1995) In: Jungers P, Daudon M (eds) Renal stone disease. Elsevier, Paris, pp 6–7
11. Breslau NA (1994) Pathogenesis and management of hypercalciuric nephrolithiasis. Miner Electrolyte Metab 20:328–339
12. Brocks P, Dahl C, Wolf H, Transbol I (1981) Do thiazides prevent recurrent idiopathic renal calcium stones? Lancet II:124–125
13. Brown CM, Ackermann DK, Purich DL (1994) EQUIL 93: a tool for experimental and clinical urolithiasis. Urol Res 22:119–126
14. Clark JY, Thompson IM, Optenberg SA (1995) Economic impact of urolithiasis in the United States. J Urol 154:2020–2024
15. Curhan GC, Willet WC, Rimm EB, Stmpfer MJ (1993) A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med 328:833–838
16. Drach GW (1992) Urinary lithiasis: epidemiologic aspects. In: Walsh PC, Retik AB, Stamey TA, Vaughan Jr. ED (eds) Campbell's urology, vol 3. WB Saunders, Philadelphia, pp 2086–2092
17. Fleisch H (1978) Inhibitors and promoters of stone formation. Kidney Int 13:361–371
18. Fuss M, Pepersack T, Bergmann P, Hurard T, Simon J, Corvilain J (1990) Low calcium diet in idiopathic urolithiasis: a risk factor for osteopenia as great as in primary hyperparathyroidism. Br J Urol 65:560–563
19. Haggit RC, Pitcock JA (1971) Renal medullary calcifications: a light and electron microscopic study. J Urol 106:342–347
20. Harvey JA, Hill KD, Pak CYC (1989) Epidemiology of stone disease in the United States as discerned from a stone-risk profile. In: Walker VR, Sutton RAL, Cameron ECB, Pak CYC, Robertson WG (eds) Urolithiasis. Plenum Press, New York, pp 665–667
21. Herrmann U, Schwille PO (1992) Crystalluria in idiopathic recurrent calcium urolithiasis: dependence on stone composition. Urol Res 20:157–164
22. Hess B, Kok DJ (1996) Nucleation, growth and aggregation of stone-forming crystals. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM (eds) Kidney stones: medical and surgical management. Lippincott-Raven, Philadelphia New York, pp 3–32
23. Hess B (1994) Tamm-Horsfall glycoprotein and calcium nephrolithiasis. Miner Electrolyte Metab 20:393–398

24. Hofbauer J, Höbarth K, Szabo N, Marberger M (1994) Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis: a prospective randomized study. Br J Urol 73:362–365
25. Hofbauer J, Höbarth K, Ludvik G, Marberger M (1994) The "stone clinic effect": myth or reality? Eur Urol 26:309–313
26. Hojgaard I, Fornander A, Nilsson M, Tiselius HG (1997) Crystallization during volume reduction of solutions with a composition corresponding to that in the collecting duct. The influence of hydroxyapatite seed crystals and urinary macromolecules. Scanning Microsc (in press)
27. Holmes RP, Assimos DG, Goodman HO (1997) Genetic and dietary influences on urinary oxalate excretion. Urol Res (in press)
28. Howard JE, Thomas WC (1958) Some observations on rachitic rat cartilage of probable significance in the etiology of renal calculi. Trans Am Clin Climatol Assoc 70:94–102
29. Jungers P, Lioté F, Houillier P, Labrunie M, Hennequin C, Lacour B, Daudon M (1997) Vertrebal bone mineral density in recurrent calcium stone formers with absorptive or renal idiopathic hypercalciuria. In: Jungers P, Daudon M (eds) Renal stone disease. Elsevier, Paris, pp 188–189
30. Kavanagh JP (1992) Methods for the study of calcium oxalate crystallization and their application to urolithiasis research. Scanning Microsc 6:685–705
31. Khan SR (1995) Heterogeneous nucleation of calcium oxalate crystals in mammalian urine. Scanning Microsc 9:597–616
32. Khan SR (1995) Calcium oxalate crystal interaction with renal tubular epithelium, mechanism of crystal adhesion and its impact on stone development. Urol Res 23:71–79
33. Kok DJ, Khan SR (1994) Calcium oxalate nephrolithiasis: a free or fixed particle disease? Kidney Int 46:847–854
34. Nakagawa Y, Abram V, Parks JH, Lau HSH, Kawooya JK, Coe FL (1985) Urine glycoprotein crystal growth inhibitors: evidence for a molecular abnormality in calcium oxalate nephrolithiasis. J Clin Invest 76:1455–1462
35. Pak CYC, Hayashi Y, Finlayson B, Chu S (1977) Estimation of the state of saturation of brushite and calcium oxalate in urine: a comparison of three methods. J Lab Clin Med 89:891–901
36. Prien EL (1975) The riddle of Randall's plaques. J Urol 114:504–507
37. Robertson WG, Scurr DS, Sergeant VJ (1985) Ionic and macromolecular modifiers of crystallization of calcium salts in urine. Fortschr Urol Nephrol 23:1–11
38. Robertson WG, Peacock M (1980) The cause of idiopathic calcium stone disease: hypercalciuria or hyperoxaluria? Nephron 26:105–110
39. Robertson WG, Heyburn PJ, Peacock M, Hanes FA, Swaminathan R (1979) The effect of high animal protein intake on the risk of calcium stone-formation in the urinary tract. Clin Sci 57:285–289
40. Robertson WG, Peacock M, Nordin BEC (1969) Calcium crystalluria in recurrent renal stone formers. Lancet II:21–24
41. Rodgers AL (1995) Promoters and inhibitors (introduction). In: Rao PN, Kavanagh JP, Tiselius HG (eds) Urolithiasis: consensus and controversies. South Manchester University Hospitals, Manchester, pp 101–109
42. Ryall RL (1995) Macromolecules in stones: promiscuous players, inadequate protectors or malevolent provocateurs? In: Tiselius HG (ed) Renal stones. Akademitryck, Edsbruk, pp 9–15
43. Ryall RL, Grover PK, Doyle IR, Harnett RM, Hibberd CM, Edyvane KA, Marshall VR (1988) The effect of macromolecules on the crystallization of calcium oxalate in human urine. In: Martelli A, Buli P, Marchesin B (eds) Inhibitors of crystallization in renal lithiasis and their clinical application. Acta Medica, Rome, pp 51–56
44. Sheehan ME, Nancollas GH (1980) Calcium oxalate crystal growth: a new constant composition method for modelling urinary stone formation. Invest Urol 17:446–450
45. Siener R, Scharrel O, Hesse A (1997) Results of metaphylaxis in 238 calcium oxalate stone formers. In: Jungers P, Daudon M (eds) Renal stone disease. Elsevier, Paris, pp 195–196
46. Sierakowski R, Finlayson B, Landes RR, Finlayson CD, Sierakowski N (1978) The frequency of urolithiasis in hospital discharge diagnoses in the United States. Invest Urol 15:438–441
47. Smith LH, Jenkins AD, Wilson JWL, Werness PG (1984) Is hydroxyapatite important in calcium urolithiasis? Fortschr Urol Nephrol 22:193–197
48. Tiselius HG (1996) Solution chemistry of supersaturation. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM (eds) Kidney stones: medical and surgical management. Lippincott-Raven, Philadelphia New York, pp 33–64
49. Verkoelen CF, Romijn JC, de Bruijn WC, Boevé ER, Cao LC, Schröder FH (1995) Association of calcium oxalate monohydrate (COM) crystals with MDCK cells. Kidney Int 48:129–138
50. Vermeulen CW, Lyon ES, Gill WB (1964) Artificial urinary concretions. Invest Urol 1:370–375
51. Williams RE (1963) Long-term survey of 538 patients with upper urinary tract stone. Br J Urol 35:416–437