Published in final edited form as:

BJU Int. 2009 May ; 103(9): 1238–1246. doi:10.1111/j.1464-410X.2008.08170.x.

Evidence for durable kidney stone prevention over several decades

Joan H. Parks and Fredric L. Coe

Renal Section, University of Chicago School of Medicine, Chicago, IL, USA

Abstract

Objective—To analyse three outcomes of stone prevention strategies in one clinic devoted to that activity since 1969, i.e. stone recurrence rates, stone-related procedures and 24-h urinary stone risk factor, to assess whether such treatment can be maintained over long periods.

Patients and methods—We selected 2509 patients with at least one laboratory follow-up after initial clinical and laboratory evaluation. We divided them into five time cohorts of 5, 10, 15, 20 and > 20 years of follow-up. Rates of new stones and stone-related procedures, and 24-h urinary stone risk factors were compared between the cohorts using analysis of variance and general linear modelling.

Results—Stone rates and rates of stone-related procedures declined in all five cohorts, as did 24-h urinary stone risk indices. We found no diminution of treatment effects for any of these three over time.

Conclusion—Those patients who remained under active care had significant reductions in stone recurrence and rates of stone-related urological procedures for up to > 20 years. However, only a small fraction of patients who entered the clinic remained for such long periods. Urine testing substantiates impressive and sustained reductions in supersaturation, the principle driving force for stone formation. Overall, for those patients willing to remain in continuous treatment for periods of up to three decades, medical stone prevention appears to be effective in maintaining low recurrence and procedure rates.

Keywords

kidney stones; recurrence; medical treatment

Introduction

At least seven prospective, controlled, double-blind randomized trials document the effectiveness of treatment measures for calcium renal stones. Three trials concern the efficacy of thiazide [1–3], two of potassium citrate [4,5], and one of allopurinol for preventing calcium stones [6] in hyperuricosuric subjects. In addition, reduced protein and sodium intake was successful in reducing calcium stone recurrence in men with hypercalciuria [7]. This primary evidence is one foundation of contemporary protocols for stone prevention.

Correspondence: Fredric L. Coe, Renal Section MC 5100, 5841 South Maryland Ave., Chicago IL 60637, USA. f-coe@uchicago.edu.

Conflict of interest

Fredric L Coe receives honoraria from LabCorp.

The other foundation is a group of treatments that have not been studied in randomized controlled trials, but have reasonable scientific evidence supporting them. Increasing urinary pH is widely used to prevent uric acid stones [8], because urinary undissociated uric acid, that comprises most uric acid stones, decreases steeply as pH increases above its pK of 5.35. The sodium, potassium and ammonium salts of uric acid that predominate at a pH of ≥ 6 are soluble enough that such stones are not often encountered. High urinary volume and pH and thiol binding agents are established and rational methods for preventing cystine stones [9], as is parathyroidectomy for primary hyperparathyroidism with stones [10]. The use of a low-fat diet and cholestyramine to lower urine oxalate excretion in enteric hyperoxaluria is an unproven but reasonable approach [11], as is reduced diet oxalate and avoidance of low-calcium diets in patients with hyperoxaluria not due to bowel disease [12].

What trials and laboratory research cannot confirm, and what is lacking in descriptive reports of treatment effects thus far, is how durable stone prevention can be, whether or not it continues for many years in actual treatment programmes. A trial rightly concerns one agent for a modest time, generally 3–5 years, used for highly selected patients. Reports of individual treatments outside of formal trials are much the same. However, in clinical practice, many methods can be used over time, with the goal of reducing recurrence for decades. We present here clinical observations over up to 30 years among patients enrolled in a stone-prevention programme begun in 1969 and run continuously thereafter. Our primary objective was to test the hypothesis that stone prevention can be effective over such long periods. Our secondary objective was to test the hypothesis that abnormalities in urinary chemistry thought to promote stones can be controlled over the same intervals. We know of no other reports of outcome data from such long-term treatment.

Patients and methods

From our registry of stone patients we selected 2509 (867 female) who had at least one laboratory follow-up after initial clinical and laboratory evaluation. We included patients with bowel disease (160, 55 female), renal tubular acidosis (14, nine female), hyperparathyroidism (103, 59 female), other rare conditions (85, 44 female) and cystine stones (38, 24 female). We divided them into cohorts of 0–5 (1342, 504 females), 5–10 (515, 160 female), 10–15 (313, 94 female), 15–20 (171, 53 female) and > 20 years (168, 56 female) of follow-up. Reporting of human subject data for this work was approved by our institutional review board (Protocol #11943 A). The type of stones formed was determined as follows: calcium oxalate (CaOx) stone-former, $> 50\%$ CaOx on average of all stones; calcium phosphate (CaP) stone-former, $> 50\%$ CaP on average of all stones; uric acid (UA), cystine and struvite stone-former, any UA, cystine, or struvite in any stone (the last three, although approximate, are a suitable category in practice).

All patients were evaluated with three 24-h urine collections with corresponding fasting blood samples before treatment, and with subsequent measurements during treatment. For this report we considered the pretreatment basal measurements and the last laboratory follow-up during treatment. We measured in all urine samples: volume, calcium, magnesium, oxalate, phosphate, pH, uric acid, sodium, potassium, chloride, creatinine; in most (after 1976) we also measured citrate, sulphate, ammonia and calculated supersaturation (SS) with respect to CaOx, CaP and UA, using an established open-source software (EQUIL 2). In blood we measured calcium, phosphate, uric acid, creatinine, magnesium, sodium potassium, chloride and CO_2 content.

The computer records contained stone numbers, urological procedures, stone analyses and summary of X-ray readings by ourselves. Because urological procedures for stones have been changing over the decades included in this report, we considered cystoscopy, open

surgery, ureteroscopy, ESWL, and percutaneous removal as procedures, and did not differentiate among them in the analysis. Hospitalization criteria and patterns have also changed through the decades so we did not show hospitalization details.

Of the 1667 patients with analysed stones, 1298 had CaOx, 168 CaP, 37 cystine, 29 struvite and 135 UA. By CaOx or CaP we mean that more than half the stone was that mineral; by UA we mean any stone that contained any uric acid; by cystine we mean cystine stones in hereditary cystinuria; by struvite we mean any struvite in any stone. Obviously many patients formed admixed stones, and changing stones over such long periods as we report here; even so, the numbers presented adhere strictly to these criteria.

All patients were treated to prevent new stones. Our primary aim was to maintain SS as low as possible for CaOx, CaP and UA and (where relevant) cystine. High fluids and reduced sodium intake were recommended for virtually all patients. Thiazide diuretics were used to lower urinary calcium, potassium citrate to raise urinary pH and/or urinary citrate, allopurinol to lower urinary UA in hyperuricosuric CaOx stone formers, and combinations of these therapies, as guided by laboratory abnormalities [12]. Enteric hyperoxaluria was treated using calcium supplements with meals, cholestyramine, and reduced fat and oxalate diet. Primary hyperparathyroid disease was treated with parathyroidectomy. Cystinuria was treated with very high fluid intake, alkalinization of urine to achieve a pH of > 7.4 and thiol-binding agents when needed [13]. Treatments varied over the years, as urinary chemistry changed, and we do not attempt to detail here the changing patterns of treatment among patients. As is apparent from the distribution of patients, the magnitude of stone reduction is mostly influenced by the treatment of calcium stones in patients with no systemic disease. Even so, we felt it was worthwhile to include the complex and recalcitrant diseases such as cystinuria and enteric hyperoxaluria, as opposed to selecting subgroups. Although the range of treatments might vary widely for a given patient, this particular goal (maintenance of low SS) was a constant feature that guided treatment.

Of the 2509 patients reported here, we have complete medication records for 2149. Of these, 1336 (62%) were given thiazide, 1332 (62%) were given some form of potassium alkali, and 274 (13%) received allopurinol. Potassium chloride supplements were needed in 256 (12%) patients and amiloride in 192 (9%). Thiazide was always used only for hypercalciuria with calcium stones; amiloride and potassium chloride were used exclusively to remedy thiazide induced hypokalaemia. Potassium alkali was used as a primary treatment for hypocitraturia, to increase urinary pH in patients with any UA in any stone, and as a potassium supplement for those on thiazide who would also benefit from the alkali. Thirty-four patients, all with enteric hyperoxaluria, received cholestyramine. Twelve patients with cystinuria received a thiol-binding drug.

We used all available outside records and radiographs to assess stone and procedure numbers and rates over time. During treatment, both at times of laboratory follow-up and intervals between with clinical visits or other communications (telephone calls, emails, letters) we accumulated additional information about the matters. All such data were stored in computer-readable form and used from the computer files for this work. Stones are counted as new stones when passed or removed, or visualized by radiograph, and not present on previous radiographs. Passage or removal were documented from direct patient history and medical records. Procedures are counted from operative reports or patient history, or letters from outside physicians. Radiographs were all read by the authors; for each, we drew schematic pictures showing each stone in its location. A new stone is therefore defined as passage or removal of a stone that cannot be accounted for by loss previously seen. To determine loss of a stone previously seen we need two radiographs: a previous one and one taken after passage or removal. Appearance of a stone on a radiograph that was not present

on a previous radiograph also counted as a new stone. As we read the radiographs and drew the pictures, and also took the patient history and reviewed the medical records, new stones were verified as much as possible within a clinical setting. Stone counts are the sum of all new stones before and during treatment, and taken as the sum of stones passed or removed and newly appearing on radiographs. All pretreatment information was from outside sources; we treated all patients after entry. Whatever treatments were given before we treated the patients are not included here, but they would not have been effective, given that all patients were referred to us because what was done before had not satisfied all parties concerned.

Clinical encounters before treatment (Table 1) included all recorded visits to physicians and procedures. After entry, encounters are the sum of clinical visits and laboratory visits because at each laboratory visit our technicians conducted a brief interview concerning medications and new stones.

Table analysis, survival analysis and general linear models were used to assess the data, using commercial software.

Results

At entry patients were aged 39–46 years, with slightly younger patients in the > 20-year cohort; the ages at the last laboratory measurement increased, corresponding to the mean follow-up interval (Table 2). Body weight increased modestly with age, as expected; women in the longest cohort were distinctly less heavy than others. The intensity of clinical encounters was considerable during treatment, as laboratory and clinical visits were appropriately included (methods). Only a small fraction of patients had formed one stone before entry, and most were CaOx stone formers. Throughout the programme $\approx 40\%$ of patients were of unknown stone type (difference between numbers of known stone types and total numbers of patients in each column of Table 2). Likewise, $\approx 30\%$ of patients had a positive family history of stones.

For the analysis of the number of stone and procedures, we divided patients into five cohorts representing 0–5, 5–10, 10–15, 15–20 and > 20 years of treatment with follow-up. The number of pretreatment stones per patient (Fig. 1, left panel, squares) was higher in the 0–5-year than the other four cohorts ($P < 0.01$ for all comparisons). During treatment (Fig. 1, left panel, circles), the numbers of new stones per patient was significantly reduced from before treatment for all but the > 20-year cohort (Table 2, not adjusted). The numbers next to each symbol are the numbers of stones per patient per year, calculated as the ratio of the mean number of stones per patient (the value of the point on the graph) divided by the mean duration of the pretreatment or treatment interval for that cohort (intervals are given Table 2). This rate is much lower during than before treatment for the > 20-year cohort. As expected from this comparison, when stone numbers per patient are adjusted for the pretreatment and treatment intervals (Table 2) the reduction of stones is significant for the > 20-year cohort.

The time course of stone formation during treatment (Fig. 1, right panel) was similar for all five cohorts (Mantell chi-square 3.775, $P = 0.43$; Breslow-Gehan chi-square 7.207, $P = 0.125$; Tarone-Ware chi-square 5.435, $P = 0.246$). Times to 25% relapse were 8–12 years; the 0–5-year cohort (black circles) were never < 85% stone-free. By 5 years, a common clinical benchmark time, all five groups were still 85–> 90% stone-free.

Before treatment, procedure rates of the 0–5-year cohort (Fig. 2, left panel, squares) exceeded those of other cohorts; ($P < 0.001$ vs all of the other cohorts individually). Also, the 5–10-year cohort differed from the > 20-year cohort ($P < 0.001$), i.e. pretreatment

procedure numbers were higher in the more recent than in earlier cohorts. Adjustment for numbers of stones did not alter this conclusion (results not shown).

During treatment, the number of procedures per patient (Fig. 2, left panel, circles) was lower than before treatment for all but the > 20-year cohorts if not adjusted for the interval of treatment (Table 2, procedures not adjusted). With an adjustment for duration of treatment, procedure rates were lower during treatment in all cohorts, including the > 20-year cohort (Table 2, procedures adjusted for time). This analysis is supported by a simple calculation of procedure rates per patient per year (numbers by each symbol, Fig. 2, left panel); the rate per year differed by about five times for the > 20-year cohort comparing pretreatment to treatment results. The decline in procedure rates during treatment arose only partly from the variation in stone numbers. When adjusted for numbers of pretreatment and treatment stones (Table 2) treatment procedure rates no longer differed from pretreatment rates for the > 20-year cohort, but the other cohorts were hardly changed.

In all five cohorts most procedures during the treatment interval occurred early (Fig. 2, right panel). After ≈ 3 years of treatment all five survival curves have about the same slope, but during the initial high incidence of procedures, the groups differed significantly (chi-square; Mantell, 56, $P = 0.001$; Breslow-Gehan, 48, $P = 0.001$; Tarone-Ware, 52, $P = 0.001$). Note that the x -axis is truncated at 15 years, there being no events past that time.

Urinary calcium excretion of men and women (Fig. 3, left panels, Table 3) was lowered by treatment for all five cohorts. Urinary volume was increased throughout treatment in both sexes (Fig. 3, middle panels, Table 3). Urinary oxalate excretion was mostly unchanged by treatment, despite the efforts that were made to do so (Table 3). CaOx SS decreased (Fig. 3, right panels, Table 3) and remained low throughout the entire period of observations.

Urinary pH (Fig. 4, left panel, Table 3) was increased throughout treatment in both sexes, except for one interval among women. Although the increase in pH offset the increase in urinary volume and decline in urinary calcium, CaP SS (Fig. 4 middle panels, Table 3) decreased to a significant extent in all but two instances (Table 3). Urinary citrate (not shown) increased in men (Table 3), which acted to decrease CaP SS, but this did not occur in women. UA SS decreased remarkably because of a high pH and volume (Fig. 4, right panel, Table 3); UA excretion (Table 3) was not reduced during treatment.

Serum creatinine levels were higher during treatment for all follow-up cohorts (Fig. 5, left panels, Table 3). Urinary creatinine excretion (Fig. 5, middle panels, Table 3) declined in the 15–20- and > 20-year cohorts. Creatinine clearance decreased smoothly with time and was reduced during treatment even in the earliest cohort (Fig. 5, right panels). The decline in urinary creatinine excretion was not generally paralleled by a decrease in body weight (Table 3) so the ratio of body muscle mass (marked by urinary creatinine) to weight decreased in the later three cohorts (Table 3), reflecting a replacement of muscle by fat. When creatinine clearance was adjusted not only for age at entry, but for age at the last measurement (Table 3) changes with time were reduced substantially, indicating that the decrease we observed can be mostly accounted for by age itself rather than effects of stones and their treatments.

Clinical efforts to lower sodium intake are part of our treatment protocol, but changes were very slight (Table 3), as evidenced by a nearly constant mean urinary sodium excretion that in fact increased slightly with treatment, especially in men. Serum measurements relevant to stones, including calcium, phosphate, potassium and bicarbonate showed no changes (results not shown).

Discussion

Throughout the years of follow-up stone rates were very reduced in the present patients compared to the rates before treatment. Over time, patients relapsed, so that by 20 years $\approx$ 40% had formed at least one new stone; this is much below typical relapse rates in prospective trials, of $\approx$ 60% by 3 years for placebo arms and $\approx$ 20% for active treatments [15]. Even though 40% of patients formed at least one new stone by 20 years, the total numbers of stones per patient per year decreased by five or more times, to $<$ 20% of control rates, meaning that relapse had to involve fewer than half of the stones per event before treatment.

As expected from the reduction of stones, numbers of procedures per patient were reduced except for the longest cohort. Rates per patient adjusted for years of follow-up were reduced in all cohorts. Of interest, the decline in procedure rates remained significant in four of the five cohorts (excluding the most long-term cohort) even when adjusted for numbers of stones. This implies that stones passed required fewer procedures with treatment than before treatment, perhaps a reflection of being smaller. Our data do not permit analysis of this idea. Survival curves make clear that most procedures during treatment occurred very early, within the first few years, and therefore might reflect stones formed before treatment began. Altogether, stone prevention can be durable in terms of reduced numbers of stones and stone treatment procedures.

A fairly obvious limitation of this report and of our clinical programme is that durable treatment could be documented only for those patients who stayed in the programme, and the number of patients who did so (Methods and Table 2) is a fraction of those who entered. We have presented patient loss in the past at $\approx$ 20% per year, so that within any cohort loss is log-linear proportional to time [14]. For those who mean to stay the investment of time and money to evaluate for cause of stones and initiate treatment is well worthwhile. Why people discontinue is a vexed question we have never been able to answer.

Why people stay might partly be related to their initial troubles. We noted in our survival analysis that the longest-term cohort contained people who had the most new procedures early in their treatment experience. Perhaps their motivation was to avoid more surgery. This same group did not have more procedures per patient than those in other cohorts before they entered treatment; in fact they had less, so the effect might be somehow related to the early treatment experience.

We can only speculate as to why pretreatment procedure numbers and new stone counts were highest in our most recent cohorts than in those of the past. Perhaps lithotripsy and ureteroscopy have made procedures easier and therefore more common. Possibly stone counts are inflated now, as compared to the past, with the advent of CT, a technique that reveals far more stones in the kidneys than common radiographs did. This work was not intended to explore these questions.

A well-accepted paradigm in stone disease is that stones require urinary driving forces to promote crystal formation, and that therefore reduced stone formation should be accompanied by clear evidence of a long-term reduction of such driving forces. We certainly have such evidence. Urinary calcium is reduced in the long-term, and urine volume increased, so that SS for CaOx and CaP are lowered. This lowering of SS and increase of volume are steady over decades and would be expected to reduce calcium stones. Likewise, urinary pH is generally increased by treatment, so that UA SS decreased remarkably. Our stone counts are mainly calcium and UA stones, because most of our patients formed such stones, so the decline we found is fully consistent with the laboratory changes. Urinary oxalate excretion was uninfluenced by treatment, even though reduced oxalate intake [15]

and avoidance of low calcium diet (that can increase urinary oxalate [16]) are part of our treatment plan. Reduced sodium intake was also invariably suggested as a way to lower urinary calcium [7], and like urinary oxalate we could make no effective changes in it.

It is possible that this report could be improved by an attempt to detail the actual treatments each patient received over time, but that is not the case. Whereas we specify in the Methods our general approach, one consistent with our reviews [12] and with common practice [17], and detail the fractions of patients who received the most common stone-prevention agents, individual patients received a wide variety of treatments with considerable change over the years.

No doubt the decrease in urinary calcium excretion reflected mainly thiazide use [18] and the increase in urinary pH with potassium citrate [19]. Reduced protein intake, and less sodium intake in some cases, probably also made a difference, but not on average, as urinary sodium did not decrease in general. Urinary volume increased presumably because of our efforts, but we could not document exactly how this was accomplished. Even though we have reported a substantial experience with intestinal hyperoxaluria [11], and used appropriate diet and medications to lower urinary oxalate, and even though we pursued reduced diet oxalate and increased diet calcium intake for hyperoxaluria of common stone-formers, there was no overall change in average oxalate excretion.

Perhaps the best way to envision our stone-prevention programme is as an agency for change (diet, drugs, fluids) always aiming to lower SS by whatever combination of means that would work for a given person over long periods. Perhaps the best way to interpret this report is as a reflection of such an effort, which did indeed lower SS and lead to substantial reductions of stones and stone-related procedures. Clearly, prospective trials are the basis for all of our treatments, and the only 'reference standard'. Reports such as this complement trials, in illustrating what actually happens over periods that no trial can encompass.

We have already reported age-related decrease in renal function with time, and showed that like all people, stone-formers show a progressive loss, but unlike most people their loss rate is higher in the mid years of life [20,21]. As expected, creatinine clearance adjusted for age at entry was no different at entry for the present five cohorts. Clearance declined significantly in all five male, and the three longest female cohorts. However, when clearances were adjusted for age at the last measurement, and for age at entry, virtually all differences disappeared. Put another way, with age adjustments, we could find no specific effect of being in stone treatment that reduced or maintained creatinine clearance.

Acknowledgments

Supported by NIH NIDDK P01 56788

Abbreviations

CaOx	calcium oxalate
CaP	calcium phosphate
UA	uric acid
SS	supersaturation

References

1. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J Urol.* 1988; 139:679–84. [PubMed: 3280829]
2. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. *Acta Med Scand.* 1984; 215:383–9. [PubMed: 6375276]
3. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol Suppl.* 1993; 6:S78–S86.
4. Ettinger B, Pak CY, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol.* 1997; 158:2069–73. [PubMed: 9366314]
5. Barcelo P, Wuhl O, Servitge E, et al. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol.* 1993; 150:1761–4. [PubMed: 8230497]
6. Ettinger B, Tang A, Citron JT, et al. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med.* 1986; 315:1386–9. [PubMed: 3534570]
7. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med.* 2002; 346:77–84. [PubMed: 11784873]
8. Bushinsky DA. Kidney stones. *Adv Intern Med.* 2001; 47:219–38. [PubMed: 11795076]
9. Bushinsky DA. Nephrolithiasis. *J Am Soc Nephrol.* 1998; 9:917–24. [PubMed: 9596092]
10. Silverberg SJ, Shane E, Jacobs TP, et al. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med.* 1999; 341:1249–55. [PubMed: 10528034]
11. Parks JH, Worcester EM, O'Connor RC, Coe FL. Urine stone risk factors in nephrolithiasis patients with and without bowel disease. *Kidney Int.* 2003; 63:255–65. [PubMed: 12472791]
12. Coe FL, Evan A, Worcester E. Kidney stone disease. *J Clin Invest.* 2005; 115:2598–608. [PubMed: 16200192]
13. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. *Kidney Int.* 2006; 69:1041–7. [PubMed: 16501494]
14. Parks JH, Asplin JR, Coe FL. Patient adherence to long-term medical treatment of kidney stones. *J Urol.* 2001; 166:2057–60. [PubMed: 11696706]
15. Ruml LA, Pearle MS, Pak CY. Medical therapy, calcium oxalate urolithiasis. *Urol Clin North Am.* 1997; 24:117–33. [PubMed: 9048856]
16. Matsumoto ED, Heller HJ, ms-Huet B, et al. Effect of high and low calcium diets on stone forming risk during liberal oxalate intake. *J Urol.* 2006; 176:132–6. [PubMed: 16753387]
17. Chandhoke PS. Evaluation of the recurrent stone former. *Urol Clin North Am.* 2007; 34:315–22. [PubMed: 17678982]
18. Bolland MJ, Ames RW, Horne AM, et al. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. *Osteoporos Int.* 2007; 18:479–86. [PubMed: 17120180]
19. Koff SG, Paquette EL, Cullen J, et al. Comparison between lemonade and potassium citrate and impact on urine pH and 24-hour urine parameters in patients with kidney stone formation. *Urology.* 2007; 69:1013–6. [PubMed: 17572176]
20. Worcester EM, Parks JH, Evan AP, Coe FL. Renal function in patients with nephrolithiasis. *J Urol.* 2006; 176:600–3. [PubMed: 16813897]
21. Gillen DL, Worcester EM, Coe FL. Decreased renal function among adults with a history of nephrolithiasis: a study of NHANES III. *Kidney Int.* 2005; 67:685–90. [PubMed: 15673317]

Fig. 1.

Stones per patient (left panel). Values are the mean (SEM) numbers of stones per patient before (squares) and during (circles) treatment for the five cohorts, from ANOVA that included cohort and pretreatment vs treatment period. The numbers adjacent to each symbol are numbers of stones per patient per year, and were calculated as the ratio of the mean number of stones per patient (the value of the point on the graph) divided by the mean duration of the pretreatment or treatment interval for that cohort. Numbers of stones during treatment for all but the > 20-year cohort were less than pretreatment (*P* values in Table 2) whether or not adjustment is made for the treatment and pretreatment intervals. For the > 20-year cohort the difference was significant only with adjustment for time intervals. Survival analyses (right panel); the time course of relapse was no different among the five cohorts: 75% survival quintiles (% free of procedures) were: 5–10-year, grey circles, 8.7 years; 10–15-year, black triangle, 9.9 years; 15–20-year, grey triangles, 12.9 years; > 20-year, black squares, 9.4 years; the 0–5-year cohort, black circles, was > 85% stone-free by the end of the observation period. Here and in other figures, connecting lines are for visual clarity.

Fig. 2.

Mean (SEM) stone procedures per patient (Fig. 2 left panel) are shown for treatment (circles) and pretreatment intervals (squares) for the five cohorts. The procedure rates calculated as the ratio of procedures per patient to the interval before or during treatment are shown as numbers adjacent to each plotted symbol. Procedure rates adjusted or not for the time interval were lower during treatment than before treatment except for the > 20-year cohort, where the difference was significant only with time adjustment (Table 2). This distinction is apparent from the near overlap of the circle and square for the > 20-year cohort despite a five-fold difference in the values of the procedure rates per year, numerically beside the symbols. Adjustment for both the time interval and numbers of stones formed eliminated the significance of the reduction of procedures for the > 20-year cohort, but did not change results for the other four cohorts. Survival analysis (right panel) showed a much higher rate of procedures during treatment in the > 20-year cohort and a general trend to higher rates in the later vs earlier cohorts (statistics are in the Results). After ≈ 3 years all five cohorts have reasonably similar slopes. Symbols: 0–5-year, black circles; 5–10-year, grey circles; 10–15-year, black triangle; 15–20-year, grey triangle; > 20-year, black square. Note that the x -axis runs to only 15 years as no new events occurred after that interval. Survival quintiles (% free of procedures) were 87% at 4.3 years, 82% at 4.8 years, and 75% at 4.8 years, 13.4 years, and 9.7 years, for the 0–5-, 5–10-, 19–15-, 15–20- and > 20-year cohorts, respectively.

Fig. 3.

CaOx SS; compared to pretreatment values (squares) urinary calcium (left panels) was reduced throughout treatment (circles) in both sexes (upper and lower panels) and all cohorts to a significant extent (Table 3). Urinary volume (middle panels) was also increased throughout treatment; a dotted line at 2 L (a reasonable treatment goal) is added for visual clarity. Urinary SS CaOx (right panels) was reduced throughout treatment because of reduced calcium excretion and increased volume. Urinary oxalate excretion (not shown) was not altered by treatment (Table 3).

Fig. 4.

CaP and UA SS; compared to pretreatment (squares), urinary pH (left panels) was increased during treatment (circles) except for one point at 10–15 years in women (upper left panel). The y-line at pH 6 (a reasonable urinary pH goal) is shown for visual clarity. SS CaP (middle panels) was reduced during treatment to a significant extent (Table 3) in virtually all cohorts. SS UA was reduced (right panels) throughout treatment in all cohorts (Table 3).

Fig. 5.

Serum and urinary creatinine and creatinine clearance. Serum creatinine concentrations during treatment (circles) were above pretreatment (squares) in all cohorts (left hand panels) and both sexes. Urinary creatinine excretion rates (middle panels) were somewhat reduced in later treatment intervals (Table 3). Creatinine clearance values during treatment were below pretreatment (right panels) for all of the three later cohorts. When creatinine clearance was adjusted for age at the time of measurement, these differences were markedly reduced suggesting they are mainly an age effect (Table 3 and Results).

Table 1

The clinical characteristics of the patients in the five cohorts

Characteristic	0-5		5-10		10-15		15-20		> 20	
	M	F	M	F	M	F	M	F	M	F
No. of patients	838	504	355	160	220	94	118	53	112	56
Mean (SEM):										
Age at entry, years	46 (1)	42 (1)	45 (1)	43 (1)	46 (1)	45 (1)	45 (1)	43 (1)	40 (1)	39 (1)
Age at last measurement, years	48 (1)	44 (1)	52 (1)	49 (1)	58 (1)	57 (1)	62 (1)	61 (2)	66 (1)	65 (1)
Body weight at entry, kg	88 (1)	73 (1)	84 (1)	73 (2)	84 (1)	73 (2)	83 (1)	67 (2)	82 (2)	63 (2)
Body weight at last measurement, kg	88 (1)	72 (1)	87 (1)	75 (2)	87 (1)	76 (2)	86 (1)	70 (2)	86 (2)	69 (2)
Family history of stones, %	26	26	34	28	31	23	34	21	33	27
n (%) of patients:										
Clinical encounters before entry	6 (1)	7 (1)	6 (1)	7 (1)	6 (1)	7 (1)	6 (1)	6 (1)	6 (1)	5 (1)
Clinical encounters after entry	3 (1)	4 (1)	5 (1)	8 (1)	7 (1)	9 (1)	8 (1)	10 (1)	12 (1)	15 (1)
Laboratory visits after entry	3 (1)	2 (1)	6 (1)	6 (1)	9 (1)	9 (1)	14 (1)	14 (1)	20 (1)	21 (1)
n patients										
Formed only one stone, n	147	105	60	27	31	16	24	15	23	16
CaOx stones	444	193	216	66	139	36	67	22	77	29
CaP stones	54	9	6	18	5	13	8	4	5	7
UA in stones	64	17	24	11	12	2	5	1	2	2
Cystine stones	5	14	6	5	1	1	1	2	1	1
Struvite in stones	5	9	0	3	1	4	0	3	3	3

Table 2

Stones and procedures (pre-treatment – treatment)

Mean (SEM) difference pre-treatment – treatment	Cohort				
	0–5	5–10	10–15	15–20	> 20
Number of patients	1342	515	314	171	168
Years of follow-up	1.8 (0.04)	7.1 (0.1)	12.2 (0.08)	17.4 (0.1)	25.7 (0.3)
Stones/patient (not A)	15 (1) [‡]	9 (2) [‡]	6 (3) [*]	8 (4) [*]	7 (4)
Stones/patient (A)	15 (1) [‡]	10 (2) [‡]	7 (3) [‡]	8 (4) [*]	9 (4) [*]
Procedures/patient (not A)	2.9 (0.2) [‡]	1.9 (0.2) [‡]	1.4 (0.3) [‡]	1.2 (0.4) [‡]	0.06 (0.4)
Procedures/patient (At)	2.6 (0.2) [‡]	2.1 (0.2) [‡]	1.9 (0.31) [‡]	2.1 (0.4) [‡]	1.9 (0.5) [‡]
Procedures/patient (Ais)	2.4 (0.2) [‡]	2 (0.2) [‡]	2 (0.31) [‡]	2 (0.5) [‡]	1 (1)

A, adjusted for time, i.e. interval between first stone and entry into the programme (pre-treatment) and interval from treatment onset to last contact (treatment interval); At, adjusted for time within the pre-treatment and treatment intervals; Ais, adjusted for time and numbers of stones. Differs from 0,

^{*} $P < 0.05$;

[‡] $P < 0.01$;

[‡] $P < 0.001$.

Table 3

Selected measurements (treatment – pre-treatment) in the five cohorts

Variable	0-5		5-10		10-15		15-20		> 20	
	M	F	M	F	M	F	M	F	M	F
Calcium 24-h, mg/day	-35 (5)	-23 (6)	-33 (8)	-33 (10)	-43 (10)	-42 (13)	-51 (14)	-61 (18)	-62 (14)	-73 (17)
Volume, L/day	0.42 (0.04)	0.53 (0.06)	0.48 (0.06)	0.46 (0.10)	0.52 (0.08)	0.55 (0.12)	0.38 (0.12)	0.62 (0.17)	0.6 (0.12)	0.7 (0.16)
Oxalate 24-h, mg/day	0.4 (1.0)	1.4 (1.2)	2.0 (1.0)	- 1.2 (2.1)	0.6 (2.0)	0.7 (3.0)	7.0 (3.0)	9.0 (4.0)	7.0 (3.0)	10 (4.0)
SS CaOx	-2.8 (0.2)	-3.2 (0.3)	-2.9 (0.3)	-3.7 (0.5)	-3.8 (0.4)	-3.7 (0.6)	-2.7 (0.6)	-4 (0.9)	-3.7 (0.7)	-3.7 (1.1)
pH	0.25 (0.03)	0.26 (0.03)	0.33 (0.04)	0.35 (0.06)	0.28 (0.05)	0.01 (0.08)	0.32 (0.07)	0.5 (0.1)	0.26 (0.07)	0.42 (0.11)
SS CaP	-0.20 (0.05)	-0.39 (0.06)	-0.12 (0.08)	-0.26 (0.11)	-0.48 (0.11)	-0.7 (0.2)	-0.49 (0.15)	-0.65 (0.21)	-0.96 (0.18)	-0.79 (0.26)
Citrate 24-h, mg/day	50 (16)	38 (20)	84 (26)	12 (36)	84 (35)	68 (51)	124 (48)	41 (70)	<i>142 (60)</i>	36 (86)
SS UA	-0.52 (0.05)	-0.47 (0.05)	-0.7 (0.08)	-0.55 (0.1)	-0.59 (0.1)	-0.42 (0.14)	-0.42 (0.14)	-0.66 (0.2)	-0.62 (0.17)	-0.65 (0.23)
UA 24-h, mg/day	11 (8)	21 (8)	-13 (12)	9 (14)	-16 (15)	-19 (19)	-3 (21)	15 (25)	-35 (22)	33 (24)
Serum creatinine, mg/dL	0.06 (0.02)	<i>0.04 (0.02)</i>	0.07 (0.02)	<i>0.06 (0.03)</i>	0.08 (0.03)	0.13 (0.04)	0.15 (0.04)	0.2 (0.05)	0.14 (0.04)	0.15 (0.05)
Creatinine 24-hm, mg/day	14 (20)	2 (20)	-0.14 (29)	2 (34)	-66 (38)	-96 (45)	-214 (52)	-91 (60)	-258 (53)	-122 (58)
Creatinine clearance, mL/min	<i>-3.3 (1.4)</i>	-3 (2)	-6 (2)	-6 (3)	-10 (3)	-16 (4)	-23 (4)	-21 (6)	-26 (4)	-23 (5)
Adjusted for age	-2 (1)	-2 (2)	0.4 (2)	-2 (3)	0.6 (3)	-8 (4)	-9 (4)	-11 (6)	-4 (4)	-8 (5)
Creatinine, mg/kg body weight	0.07 (0.2)	-0.38 (0.28)	-0.52 (0.26)	-0.28 (0.49)	-1.5 (0.3)	-2 (0.6)	-3.1 (0.5)	-2.2 (0.8)	-4.2 (0.5)	-3.7 (0.8)
Body weight, kg	0.5 (0.8)	-0.6 (1.3)	2.0 (1.0)	1.6 (2.2)	3.0 (2.0)	3.8 (2.9)	2.0 (2.0)	3.9 (3.9)	4.0 (2.0)	6.6 (3.8)
Na 24-h, mmol/L	9 (3)	18 (4)	16 (5)	<i>14 (6)</i>	18 (6)	12 (8)	<i>20 (9)</i>	13 (11)	6 (9)	<i>22 (11)</i>

All values are mean (SEM) differences (treatment – pre treatment). Differs from 0, bold *P* < 0.01, italic < 0.05.