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Original Article

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Urine pH in renal calcium stone formers who do and do not increase stone phosphate content with time

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Abstract

Background. Calcium phosphate (CaP) renal stones appear to be increasing in prevalence, and are caused by high urine CaP supersaturation, which arises from genetic hypercalciuria and high urine pH. Renal damage from stones or procedures, or treatments for stone could raise urine pH; alternatively pH may be intrinsically high in some people who are thereby predisposed to CaP stones.

Methods. To distinguish these alternatives we sequenced changes in urine pH and stone CaP content asking which occurs first in patients whose stones showed progressive increase in CaP over time. From 4767 patients we found 62 in whom we could document transformation from calcium oxalate (CaOx) to CaP stones, and 134 CaOx controls who did not transform. Laboratory and clinical finding were contrasted between these groups.

Results. Even when patients were forming relatively pure CaOx stones, those destined to increase stone CaP had higher urine pH than controls who never did so. Their higher pH was present before and during treatments to prevent new stone formation. Shock wave lithotripsy was strongly associated with increasing stone CaP but urine pH bore no relationship to number of procedures.

Conclusion. We conclude that high pH may not be acquired as a result of stones or their treatments but may precede transformation from CaOx to CaP stones and arise from diet or possibly heredity.

Keywords: calcium phosphate; kidney stones; lithotripsy; urine pH

Introduction

Most calcium stones are composed primarily of calcium oxalate (CaOx) [1]. Stones composed primarily (>50%) of calcium phosphate (CaP) are less common [2] and seem preferentially likely in women; we found that 47% of CaP stone formers (SF) were female, compared with only 26% of CaOx SF. Idiopathic CaOx SF have no evidence of renal epithelial cell injury on papillary biopsy [3], while CaP SF plug their inner medullary collecting ducts (IMCD) and ducts of Bellini with apatite crystals [4]. For this reason, formation of CaP stones may well be a clinically undesirable event.

It is therefore worrisome that we [2] and others [5] have noted an increase in the prevalence of CaP in stones over the past two decades. Mandel found increased CaP in recurrent stones. CaP SF have high urine CaP supersaturation (SS), due to high urine pH coupled with hypercalciuria [2]. The hypercalciuria is genetic; we do not know what causes the high urine pH nor what factors might have led to the recent increase of CaP stones.

Obstruction from stones, and urological procedures including extracorporeal shock wave lithotripsy (ESWL) [6,7] could injure renal cells and increase urine pH. CaP SF have more ESWL procedures [2] than CaOx SF, so this conjecture is plausible, but unproven. Alkaline citrate salts used for stone prevention [8] could raise IMCD lumen fluid pH and CaP SS. Formation of initial CaP deposits could lead to a vicious cycle of IMCD cell injury, rising pH and more CaP deposition. An alternative possibility is that high urine pH is primary, in other words that some patients, presumably by heredity, tend to have a higher urine pH than others and are at corresponding risk for CaP stones.

One way to advance the problem is via temporal sequencing: Is high urine pH evident prior to formation of CaP stones? Is exposure to ESWL associated with subsequent increased urine pH and subsequent formation of CaP stones? While '*post hoc ergo propter hoc*' is no proof of cause, the opposite is decent disproof. We have therefore compared CaOx SF who did and did not increase their stone CaP percent (CaP%) by 20% or more, asking if urine pH of those who did exceeded that of those who did not.

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Subjects and methods

Patients

Idiopathic calcium SF From our database of 4767 patients, we selected those who had two or more stone analyses, complete initial laboratory evaluation and clinical follow-up data. Patients with any uric acid, struvite or cystine in any of their stones were eliminated as were patients with hyperparathyroidism, bowel disease, renal tubular acidosis and any other systemic stone forming diseases. Patients with reduced creatinine clearance or increased serum creatinine were excluded. We found 445 patients (126 female) who met these criteria. The analysed stones may have been passed either before or after entry into our program.

Transformers From the 445 patients, we selected all who had an initial stone with >50% CaOx, and had a last stone with a CaP% at least 20% higher than that of their first stone. We called these 62 patients (14 female) transformers (T). For our analysis of ESWL in relation to transformation, we used all 62 patients.

Transformers whose 24-h urine studies preceded transformation From these 62, we selected those 26 (5 female) who had their initial (pre-treatment) laboratory evaluation in our program before they passed the stone that had increased in CaP content. This means that all stones to that date had been at least 51% CaOx. We called these TP patients.

Thus, while all patients had laboratory evaluation pre-treatment, only TP had their initial laboratory evaluation prior to documented transformation of their stones to increased CaP content.

Controls, who did not transform From the original 445 idiopathic calcium SF for whom we had complete data, we selected a control group (C), whose first stones were >90% CaOx and who increased their stone CaP by <20% between the first and last analysed stone; 181 patients (134 men and 47 women) met this criteria. Of note, 54 of the original 445 calcium SF had >50% CaP in their first stone, and of these 28 (52%) were women, compared to only 23% of T and C. These 54 patients were excluded from further analyses, as were the other 148 patients from the original group of 445 who did not meet our stringent criteria for the presence or absence of transformation.

Stone analysis

As we have detailed elsewhere [9], we enter into our database only stone analyses where we have date and percent of stone minerals. We do not use chemical analyses. The dates we enter are from the analyses themselves, rather than from recollection of the patient as to when they passed the stone.

Laboratory evaluation

All patients are evaluated by a pre-treatment laboratory protocol of three 24-h urines, each with a fasting blood sample drawn between 7 and 9 am on the morning of completion of the collection, detailed elsewhere [9]. Patients are asked to discontinue medications that affect mineral balance for 2 weeks before our evaluation. They are instructed to eat and drink in the same manner as when they formed stones. Our protocol calls for a first laboratory follow-up ∼6 weeks after the start of treatment, and monitoring of blood and urine every year thereafter.

Clinical analysis

For the pre-treatment and treatment periods, we record numbers and dates of cystoscopy, ESWL, open surgery, ureteroscopy and percutaneous nephrolithotomy as well as numbers and dates of new stones, hospitalizations, infections and emergency room visits. Stone number is ascertained through patient recollection of stone passage and counting of stones on radiographs. Dating of events is an amalgam of paper records and patient recollection. Likewise, we record all medications prescribed by us or others. At each laboratory visit, medications are reviewed and the patient is instructed as to changes in diet or medication that are needed to lower stone risk.

Calculations and statistical analysis

CaOx, CaP and uric acid SS were calculated using EQUIL2. Comparisons between C, T and TP used *t*-tests. Effects of confounders such as age, sex, duration of stone disease and numbers of stones and laboratory variables that included urine creatinine, and other urine variables were assessed using general linear models. Events were analysed using multi-way χ^2 and survival analysis (Systat Corp., San Jose, CA, USA). Means are ± SEM.

Results

Comparison of urine and stone measurements between T and C

By selection, C produced last stones with much lower CaP% than T (Figure 1, upper-left panel, grey triangles). Initial stones of T (leftward group of circles) all had CaP abundances <50% (mean value was 12%), whereas last stones of T averaged 75% CaP. As a corollary (Figure 1, upper-middle panel), change in CaP% was marked in T (circles) and not different from 0 in C (triangles). Pre-treatment urine pH values of T far exceeded those of C (Figure 1, upper-right panel). During treatment, urine pH of T (Figure 1, lower-left panel) remained above C, although pH rose in both groups. As expected from the pH values, SS CaP was higher pre-treatment in T versus C (Figure 1, lower-middle panel) as well as during treatment (Figure 1, lower-right panel); this could account for their higher CaP% both in first and last stones.

Pre-treatment, urine volume and calcium and oxalate excretions of T exceeded C; because of the higher urine pH

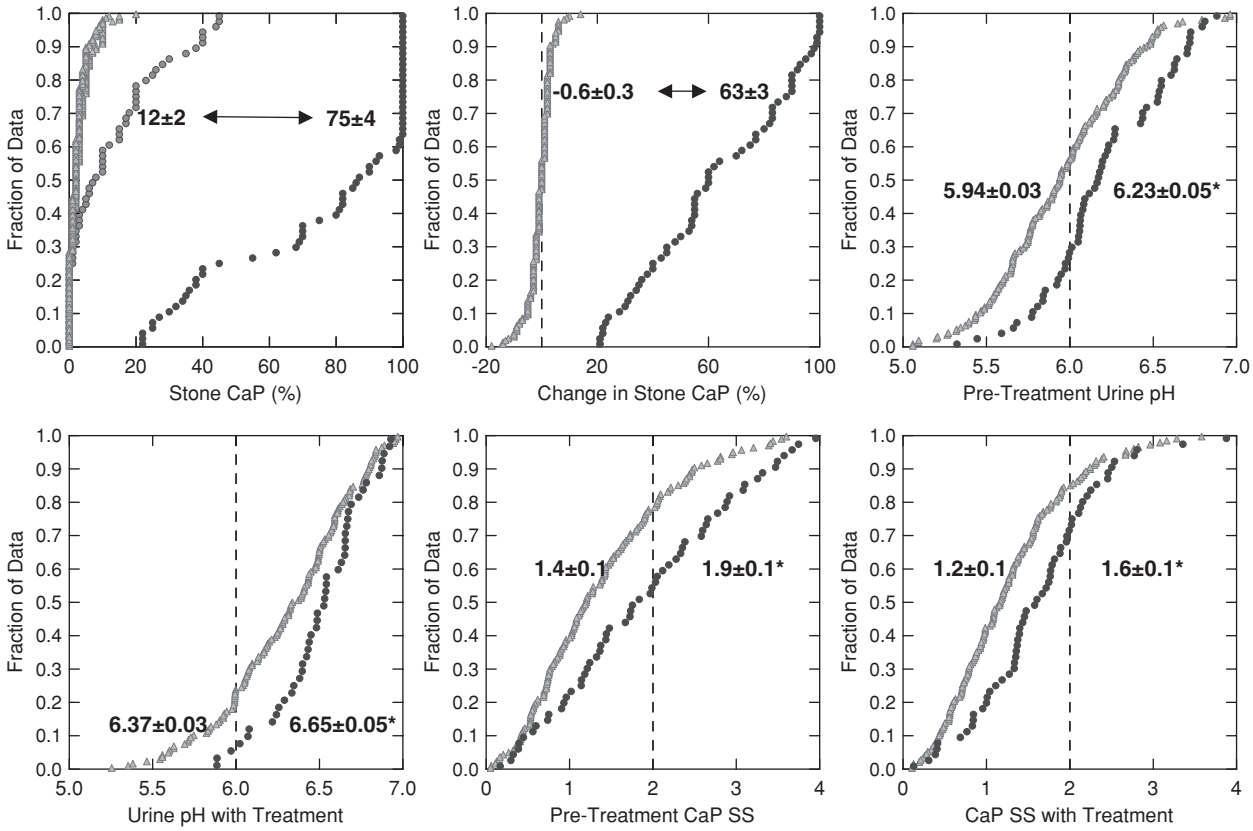

Fig. 1. Quantile plots of 62 transformers (T) (circles) and 181 calcium oxalate stone formers (CaOx SF) controls (C) (triangles). Calcium phosphate (CaP%) (*x*-axis, upper-left panel) rises greatly between first and last stones (grey and black circles) in T (mean values shown on the graph) but not in C (mean CaP% for C are 3 ± 0.3 versus 2.4 ± 0.2, first and last stone, respectively). Change in stone CaP% (upper-middle panel) in T greatly exceeded that in C, in whom no significant change occurred. Pre-treatment and during treatment urine pH (upper-right and lower-left panels) of T exceeded that of C. Pre-treatment and during treatment calcium phosphate supersaturation (SS CaP) (lower-middle and lower-right panels) of T exceeded that of C (*$P < 0.01$). Mean values are shown ± SEM.

already noted, SS for uric acid was lower in T (Table 1). During treatment, urine calcium and volume of T exceeded C [228 ± 10 versus 192 ± 6 and 2.5 ± 0.1 versus 2.2 ± 0.1, T versus C, urine calcium (mg/day) and volume (l/day), respectively, $P < 0.01$ for both comparisons], whereas urine citrate was lower in T versus C (595 ± 34 versus 684 ± 25, mg/day, $P < 0.05$).

Comparison of urine and stone measurements between TP and C

This most stringently selected sub-group of the prior 62 patients, whose labs preceded transformation, behaved in a nearly identical manner (Figure 2). Values for stone CaP and change in stone CaP% (upper-left and middle panels), urine pH before and during treatment (upper-right and lower-left panels) and SS CaP before and during treatment (lower-middle and lower-right panels) showed nearly identical means and *P*-values to those in Figure 1 (legend to Figure 2), except that CaP SS during treatment did not differ between the two groups (Figure 2, lower-right panel). Likewise, pre-treatment urine oxalate and phosphate of TP exceeded C (Table 1). During treatment, urine volume (l/day) and phosphate excretion (g/day) of TP exceeded C (2.63 ± 0.16 versus 2.16 ± 0.05 and 1.08 ± 0.05 versus 0.96 ± 0.02, TP versus C, for urine volume and phosphate excretion, respectively, $P = 0.03$ and 0.04). Urine citrate

Table 1. 24-h urine measurements at baseline

	Controls (181)	Transformers (T) (62)	Transformers (TP) (26)
Calcium (mg/day)	237 ± 99	291 ± 14***	287 ± 118
Volume (l/day)	1.6 ± 0.7	2.1 ± .1***	1.9 ± 1
Oxalate (mg/day)	40 ± 14	44 ± 1*	45 ± 10*
Phosphate (mg/day)	958 ± 294	1027 ± 34	1088 ± 281*
Citrate (mg/day)	566 ± 287	507 ± 40	547 ± 294
Creatinine (mg/day)	1711 ± 423	1779 ± 56	1861 ± 491
SS CaOx	9.78 ± 3.9	9.683 ± 1	10.6 ± 5.3
SS UA	1.4 ± 1	0.714 ± 0.1***	0.74 ± 0.48***
Potassium (mM/day)	57 ± 18	61 ± 3	60 ± 15
Magnesium (mg/day)	102 ± 35	111 ± 4	114 ± 33
Sodium (mM/day)	179 ± 58	173 ± 6	160 ± 46
Ammonium (mM/day)	32 ± 18	32 ± 4	34 ± 17
Sulfate (mEq/day)	44 ± 19	44 ± 3	43 ± 21
Uric acid (mg/day)	670 ± 194	675 ± 23	693 ± 231

SS, supersaturation; CaOx, calcium oxalate.
***$P < 0.001$ versus controls; *$P < 0.05$; values are ± SEM.

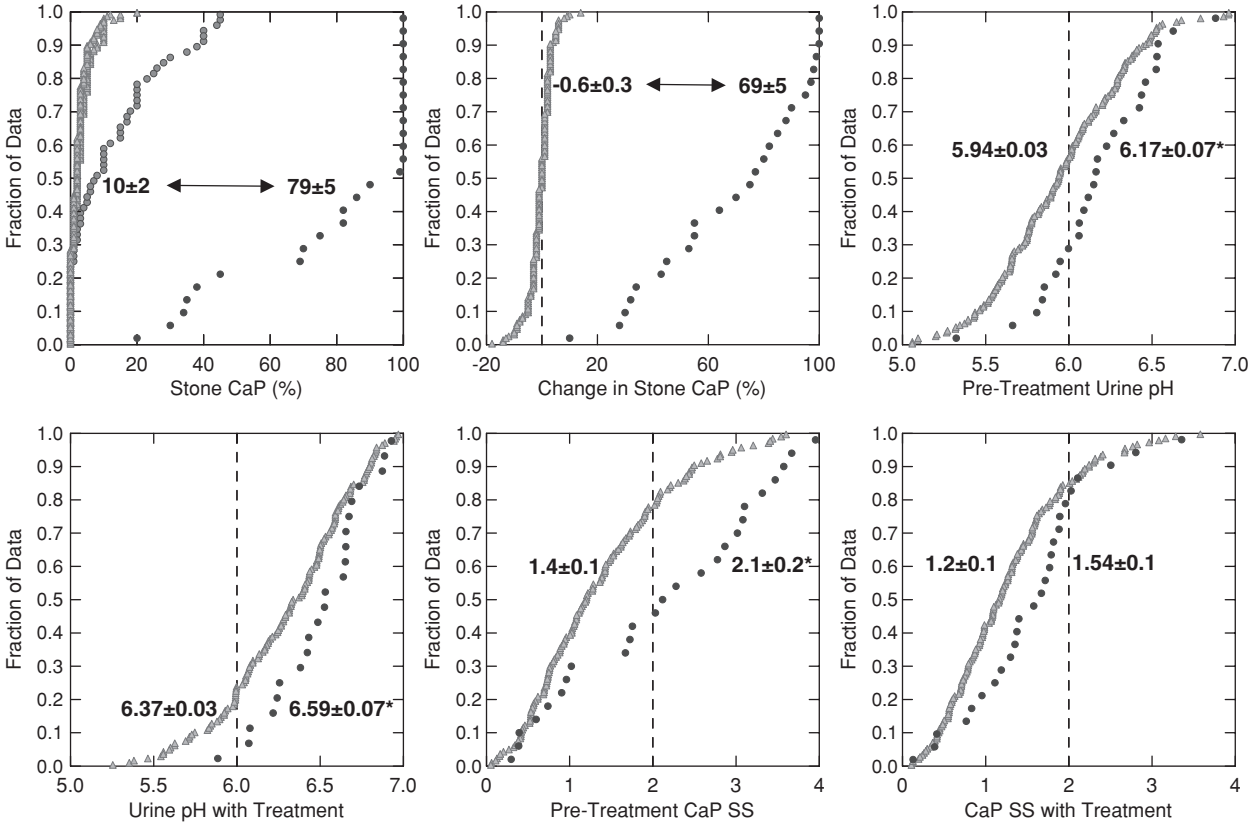

Fig. 2. Quantile plots of 26 transformers whose laboratory studies preceded addition of 20% or more stone CaP (TP) and the 181 CaOx SF controls shown in Figure 1. CaP% (*x*-axis, upper-left panel) rises greatly between the first and last stones (grey and black circles) in TP (mean values shown on the graph) but not in C (copied from Figure 1 for illustration). Change in stone CaP% (upper-middle panel) in TP greatly exceeded that in C; *P*-values for change versus 0 were <0.001 and NS, TP and C, respectively. Pre-treatment and during treatment urine pH (upper-right and lower-left panels) of TP exceeded that of C. Pre-treatment and during treatment SS CaP (lower middle and lower right panels) of TP exceeded that of C (*$P < 0.01$). Mean values are shown ± SEM.

excretions (mg/day) did not differ (624 ± 60 versus 684 ± 25, $P = 0.36$, TP versus C, respectively).

The changes seen for all 62 transformers validly reflected those seen in the hand-selected sub-group of 26 TP patients. Therefore for the whole group, as for the sub-group, urine pH and SS CaP were higher in those destined to transform than in controls, when patients destined to transform were (in the 26 cases, at least) forming stones that contained >50% CaOx. Of note, none of these cases had renal tubular acidosis, and none had overt reduction of creatinine clearance.

Table 2. ESWL in controls and transformers

ESWL	C	T	All
0	112 (62)	24 (39)	136 (56)
1	33 (18)	11 (18)	44 (18)
2	15 (8)	7 (11)	22 (9)
>2	21 (12)	20 (32)	41 (17)
All	181	62	243

C, patients who did not add >20% CaP to stones; T, patients who added >20% CaP to stones; ESWL, extra corporeal shock wave lithotripsy. Numbers of patients are shown as total (%); $\chi^2 = 17$, $P < 0.001$.

ESWL

All 62 transformers could be used for this analysis. The number of ESWL procedures was higher among T versus C (Table 2). Eighty-three percent of subjects with no ESWL procedures were C (112/136) whereas only 48% of patients (21/41) with >2 ESWL procedures were C ($\chi^2 = 17$, $P < 0.0001$ for the overall analysis of the 4 ESWL groupings). ESWL can be a response to CaP stones, especially those containing brushite, which is harder to disrupt than other stones [10]. However, our last stone analyses, showing a predominance of CaP, occurred mainly after the last ESWL (Figure 3, left panel) as shown by the leftward displacement of the star symbols (last ESWL) versus the closed circles (dates of highest CaP stone analysis). We quantified this further by calculating the time from last ESWL to last stone analysis, essentially the time duration between the stars and circles (Figure 3, right panel). A majority of intervals are >0, meaning that the ESWL preceded the last CaP stone. At least within the information available here, ESWL procedures occurred before transformation.

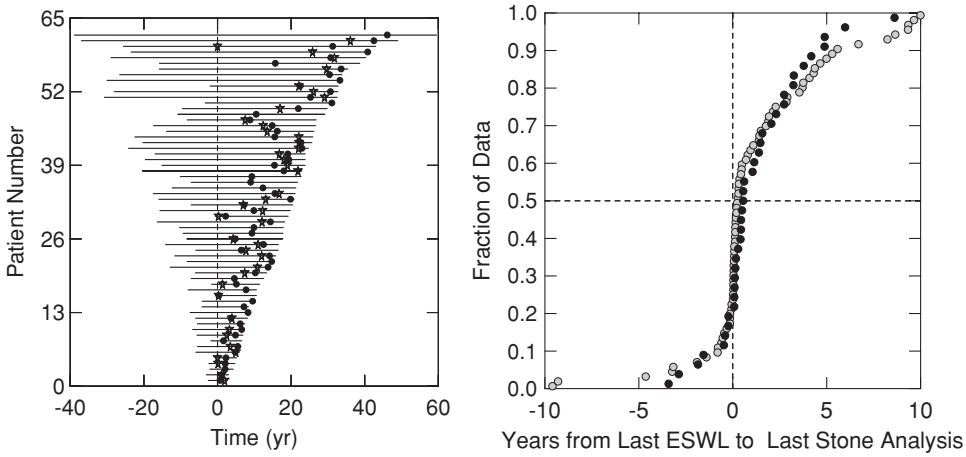

Fig. 3. Evidence that ESWL preceded analysis of the final stone that defined them as transformers. The last ESWL procedure (left panel, stars) for each of the 62 T who had an ESWL in general preceded the final (≥20% gain of CaP) stone analysis (left panel, black circles). Time (*x*-axis) is calculated from date of entry into our program (dashed vertical line). The difference in years between the last ESWL and last stone analysis (right panel) for C (grey circles) and T (black circles) who had ESWL procedures was in general >0 (vertical line); C and T did not differ with respect to this timing (overlap of the two distributions).

Before and during treatment, the 62 T and 26 TP had significantly more ESWL than C (Table 3). This was not related to higher numbers of stones, which were similar in both groups during a given interval, nor to differences of intervals, which were the same for all comparisons. Both stone number and number of ESWL fell during the treatment period in all groups, as expected. Of passing note, numbers of surgical procedures were higher in T versus C both before and during treatment (Table 3). Numbers of hospitalizations, infections, percutaneous nephrolithotomy, ureteroscopy and emergency room visits were not different either before or after entry into the program (not shown).

Table 3. Pre- and post-treatment measurements

	Controls (C)	Transformers (T)	Transformed post-entry (TP)
Pre-treatment			
Interval (years)	12.6 ± 0.7	12.5 ± 1.2	12.2 ± 2.0
Stones (number/patient)	26.7 ± 7.9	35.7 ± 16.4	19.7 ± 5.5
ESWL (number/patient)	0.7 ± 0.2	2.0 ± 0.3***	1.7 ± 0.3***
Surgery (number/patient)	0.3 ± 0.1	0.6 ± 0.1*	0.6 ± 0.2
Post-treatment			
Interval (years)	7.7 ± 0.5	8.2 ± 0.9	8.9 ± 1.4
Stones (number/patient)	1.5 ± 0.7	1.0 ± 0.3	1.2 ± 0.5
ESWL (number/patient)	0.2 ± 0.1	0.7 ± 0.1**	0.7 ± 0.2**
Surgery (number/patient)	0.02 ± 0.04	0.2 ± 0.07**	0.2 ± 0.07*

ESWL, extracorporeal shock wave lithotripsy.
Mean ± SE.
*$P < 0.05$ versus control, **$P < 0.01$, ***$P < 0.001$.
ESWL and surgery are adjusted for sex, interval and number of stones.

ESWL and urine pH are not related

We considered the possibility that multiple ESWL procedures might lead to a higher urine pH and therefore to CaP transformation. However, the pH differences, and actual urine pH values of T and C who had between 0 and >2 ESWL, before and during treatment (Figure 4, left and right panels) were not affected by the number of ESWL procedures. The pH values of the two groups were significantly different across all four ESWL sub-groups ($F = 21$, $P < 0.001$) whereas there was no effect of ESWL number in either group.

T were given more citrate and thiazide than C

By the *t*-test, the magnitude of citrate therapy in our program, expressed as citrate years per patient, did not differ (5.3 ± 0.76 versus 4 ± 0.3, T versus C, $P = 0.089$). However, when adjusted for the time of follow-up, T exceeded C (5.2 ± 0.5 versus 4 ± 0.3, T versus C, $P = 0.029$). Thiazide years were higher in T versus C by the *t*-test (7.1 ± 0.09 versus 4.9 ± 0.5, T versus C, $P = 0.037$) and when adjusted for duration of follow-up and sex (7 ± 0.6 versus 5.3 ± 0.4, T versus C, $P = 0.023$). A separate analysis for TP was not performed due to small cell size.

Discussion

Urine pH and SS CaP are higher in T versus C before transformation has occurred

Our main question appears to have an affirmative answer. In all of our transforming patients, and most importantly in those 26 patients who transformed but had not as yet passed a stone containing <50% CaOx at the time of entry into our program, we found a higher urine pH and SS CaP than in our controls, who never converted. We conclude from this that to some extent the higher pH of CaP SF [2] is not merely a result of forming such stones, but a probable antecedent. Given the extensive IMCD cell damage and interstitial fibrosis found in some CaP SF [4], this is a crucial

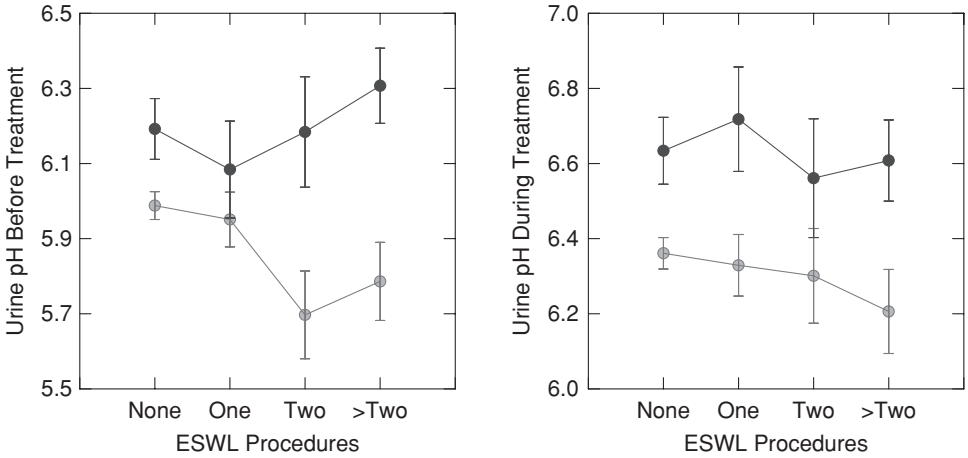

Fig. 4. Urine pH is not affected by number of ESWL procedures. Urine pH of T (black circles) and C (grey circles) measured before (left panel) and during (right panel) treatment was higher in T versus C but did not vary systematically with ESWL procedures between 0, 1, 2 and >2 (*x*-axes of both graphs).

point, because such pathology could possibly reduce final acidification of the urine. Being an antecedent, the higher pH is likelier a cause than a consequence of transformation. Although a prospective study of conversion would be ideal, it seems impractical. Among our 4767 patients, we found only 62 clear instances of conversion documented by serial stone analyses, and only 26 with labs when the person was a CaOx SF (>50% CaOx in stones). One would have to enroll many patients and follow them for an average of 7–9 years to achieve the numbers we have, and we doubt this will ever be undertaken.

Higher urine pH is not likely due to IMCD CaP deposits

In brushite SF, IMCD deposits, though locally destructive, are very sparse so that only a small fraction of any given papillum is involved [4]. Even though deposits could radically increase pH within a particular IMCD or a cluster of IMCD, they would be unlikely to damage enough IMCD cells to increase bulk urine pH. Since our T and TP patients had only 12% and 10% CaP in stones, respectively, when they entered our program, it is unlikely that subtle renal damage from deposits would have raised their 24-h bulk urine pH.

The role of ESWL is unclear

We have found ESWL associated with CaP stones [2], and now find it is also strongly associated with conversion to increased CaP in stones. Patients who transformed had significantly more ESWL than C (Table 2), both before and after entry into our program (Table 3). Dating ESWL procedures is not entirely exact to the month, though it is within a year or so. Likewise for stone analysis, we have the exact date of measurement but the date of the stone passage is often known only to the month or even year. Of course, the stone was present before it became evident in most cases. Even so, we find a majority of ESWL were completed before analysis of the first stone with at least 20% increase of CaP abundance—the stone that marks the patient as a transformer. Moreover, our patients who converted had more ESWL before they entered our program and in the case of TP when they were in fact CaOx SF with an average of 12% CaP in stones.

A clinical dose of ESWL is known to induce an acute traumatic injury to the human kidney [11] as noted by enlargement of the kidney, loss of cortico-medullary demarcation suggestive of the presence of acute internal oedema and the presence of peri-renal or sub-capsular fluid. Experimental studies in swine show that the renal papilla is the first site to sustain damage with a progression of injury that involves the vasculature in the cortex [7]. Sites of medullary injury are small in size and appear randomly positioned around the papilla. Injury is observed in adjacent blood vessels (vasa recta) and tubules. Damage to the vasa recta consists of focal lacerations through endothelial cells and their underlying basement membranes with resulting extravasations of red cells into the interstitial space. Nearby collecting ducts and loops of Henle also showed focal lacerations through the tubular lining cells and their underlying basement membranes. Extensive regions of cellular necrosis give some injured tubular segments a ghost-like appearance. The long-term sequelae to these acute sites of medullary damage are a region of scar with a loss of blood vessels and tubules [12].

Given the obvious injury potential from ESWL and the association with CaP, one might have predicted abnormal acidification and rising urine pH with an increasing number of procedures, but we did not find that. Therefore, the linkage between ESWL and conversion remains unexplained, as does the strong linkage between CaP stones and ESWL. Possibly ESWL injury predisposes to CaP deposits in renal tissue from some direct tissue effects rather than by an increase of tubule fluid pH.

T were given more citrate and thiazide than C but not clearly before transformation

Under our own care, T received more potassium citrate therapy than C. They also received more thiazide. These

two drugs are commonplace for stone prevention, and have prospective trials documenting efficacy [8], so the higher use in T versus C could well reflect a greater clinical urgency that is not documented otherwise in a specific way. Certainly, thiazide could not be imagined as promoting transformation as its main role is to lower urine calcium and therefore CaP and CaOx SS values [13]. Potassium citrate can raise urine pH and could possibly foster transformation [14]. On the other hand, citrate treatment raises urine citrate, which latter is an inhibitor of crystallization [15–19] via direct effects on crystals and binding of urine calcium. So the one effect, of pH, is generally more than offset by the benefits of the other. In T, however, we did detect an imbalance by comparison with C. Urine pH rose in all groups (T, TP and C) during treatment presumably under the influence of citrate treatment, although pH remained higher in T and TP compared to C. On the other hand, urine citrate was lower in T versus C on treatment, although not at baseline. A higher pH in T versus C, yet lower citrate, could promote crystallization and ongoing CaP stone formation. This is supported by the higher CaP SS on treatment in T compared with C. This was not true for TP, however, in whom citrate did not differ on treatment, and in whom CaP SS on treatment did not differ from C. Thus, it is not clear whether citrate treatment might be a risk factor for conversion. The presence of rising pH without an increase in citrate level may pose a risk for CaP crystal formation. This observation could be confirmed in new direct studies of pH and citrate response by CaP versus CaOx SF.

Summary

Transformation from CaOx to CaP stones may be at least in part due to high urine pH and corresponding high urine SS CaP that precedes transformation and occurs for presently unknown reasons. ESWL procedures may also contribute to transformation, perhaps via renal injury. Response of patients to potassium citrate treatment appears to differ in some patients who convert to CaP compared to those who do not convert, in that the former raise their pH but not their citrate excretion.

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Conflict of interest statement. None declared.

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