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Citrate and recurrent idiopathic calcium urolithiasis

A longitudinal pilot study on the metabolic effects of oral potassium sodium citrate administered as short-, medium- and long-term to male stone patients

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Summary. In male patients with idiopathic recurrent calcium urolithiasis (RCU) the effects of oral potassium sodium citrate (PSC) on acid-base, citrate and mineral metabolism were investigated. There were 17 normocitraturic and 15 hypocitraturic patients. The examination time points in our clinical laboratory were prior to medication and after 3, 6 and over 12 months of medication. Urine collection periods were over 24 h, 2 h – after an overnight fast – 3 h postprandially. Acceptance by the patients was poor, a large number refusing to take PSC for 12 months. Compliance of the patients continuing with the study was adequate as assessed by the urinary excretion of potassium and sodium. No unwanted side effects were observed. After 3 months of PSC medication a compensated metabolic alkalosis developed; in the urine calcium was decreased, while citrate, pH and oxalate were increased, as were hydroxyapatite supersaturation and calcium phosphate particles. After more than 12 months of PSC medication, citrate and pH tended toward the pretreatment baseline values, while hydroxyapatite supersaturation and calcium had already returned to pretreatment values. Despite ongoing PSC intake, patients with preexisting hypocitraturia had lower urinary citrate than patients with previous normocitraturia, while the concomitant pH and hydroxyapatite supersaturation in the urine of the former remained at levels close to those of the latter. Under the influence of PSC, parathyroid gland function remained unchanged, but serum levels of bone alkaline phosphatase and osteocalcin were low, and urinary hydroxyproline was high. We conclude that (1) PSC shifts the acid-base status toward metabolic alkalosis, and also modulates bone metabolism; (2) over the long term, PSC may be unable to achieve a constantly high urinary citrate, in particular in RCU with pre-existent hypocitraturia – in contrast to its short- and medium-term effects. Long-term interrupted medication with PSC is proposed for the metaphylaxis of RCU. A regimen of this type may also be expected to yield more insight into the mechanism(s) underlying hypocitraturia.

Key words: Oral potassium sodium citrate – Calcium urolithiasis – Acid-base metabolism – Mineral metabolism – Supersaturation of urine – Crystalluria

In the metaphylaxis of recurrent idiopathic calcium urolithiasis (RCU) alkali citrates are attracting increasing interest from physicians. It is felt that these substances are able to compensate for the hypocitraturia frequently seen in RCU [5, 14, 17, 25, 36] and considered a risk factor in the etiology of crystal and stone formation.

In a study on potassium citrate (PC) in RCU, we demonstrated that urinary pH, calcium and supersaturation products tended toward pretreatment values despite continuous PC administration; moreover, PC treatment appeared to be less effective in the case of pre-existent hypocitraturia, i.e. the increase in citrate in the urine was less than that with pre-existent normocitraturia [30]. In the case of PSC, too, it is still uncertain whether an adequate and sustained increase in urinary citrate and pH can be obtained. In the present work, the main aims were (1) to evaluate the short-, medium-, and long-term effects of PSC on acid-base, mineral and oxalate metabolism, physicochemical activity products and crystalluria; (2) to identify possible differences in the response of PSC-treated RCU, depending on whether the patients had pre-existent normo- or hypocitraturia.

We were able to show that in addition to acid-base and citrate metabolism, PSC also affects bone metabolism. Additionally, there are signs that the effects of PSC change during the course of its continuous administration over the long term.

Materials and methods

Study design

A cohort was studied, but the medication schedule was not fixed (see below). A control group taking placebo was not recruited. The patients gave informed consent prior to participation. Evaluation of data was prolective.

Table 1. Patient data at entry on trial

	N-Cit + H-Cit $n = 32$	N-Cit $n = 17$	H-Cit $n = 15$
Age (years)	40.8 ± 2.2 21–69	43.1 ± 2.9 21–62	38.1 ± 3.2 21–69
Body mass index $\frac{kg}{(height\ m)^2}$	25.6 ± 0.5 20–32	26.0 ± 0.6 20–32	25.2 ± 0.7 21–31
Blood pressure; mmHg			
Systolic	132 ± 4	129 ± 4	137 ± 7
Diastolic	86 ± 2	85 ± 3	86 ± 4
Normo/hypercalciuria	22 ± 10	13/4	9/6
Duration of disease (years)	12.8 ± 2.0 1–36	15.3 ± 2.9 1–36	9.9 ± 2.5 2–35
Last stone episode (< 12/> 12 months earlier)	31/1	16/1	15/0
Stones present/absent	19/13	13/14	6/9
Metabolic activity; score	12.9 ± 3.3 1–100	11.6 ± 2.8 2–50	13.6 ± 6.5 1–100

N-Cit, Normocitraturia; H-Cit, hypocitraturia
Values given are means ± SEM, with ranges below

Participants

Thirty-two male patients were assigned to the study. Women were excluded to avoid unspecific influences from the ovarian cycle [3]. The diagnosis RCU was based on criteria described earlier [30]. The intake of life-saving drugs was allowed, but not specific stone metaphylaxis.

The duration of RCU was 1–36 years. The metabolic activity of stone disease was assessed by scoring [6], which showed marked variance (score 1–100; Table 1). On entering the study, 59% of the patients had at least one concrement visible on plain X-ray of the abdomen. In all patients creatinine clearance was normal (> 60 ml/min), as was serum creatinine (< 1.4 mg/dl).

On the basis of the lower limit of normal urinary citrate in our laboratory (< 300 mg per day), the patients were broken down into a group with normocitraturia (N-Cit; $n = 17$) and one with hypocitraturia (H-Cit; $n = 15$). The total group (no breakdown by degree of citraturia) was termed N-Cit + H-Cit.

The subgroups N-Cit and H-Cit did not differ statistically with respect to age, anthropometry, blood pressure, duration of stone disease, time elapsed between the last stone episode and the first examination in our laboratory, number of patients with detectable stone or hypercalciuria (Table 1).

Study design and duration, dosage of PSC, dropouts

Four examinations in our laboratory were scheduled: before treatment and after short-term (3 months), medium-term (6 months), and long-term (> 12 months) treatment. PSC was prescribed in the form of a potassium-sodium-hydrogen-citrate (6:6:3:5) granulate (Oxalyt C; Madaus; Cologne, FRG). Apart from the days spent in the laboratory for examination, the patients went about their daily routine activities, and PSC was taken together with the usual home diet and liquids. The study was carried out on an outpatient basis, but the laboratory examination was standardized (for details of the laboratory program see [23]) and included the ingestion of a synthetic, liquid test meal supplemented with up to 1000 mg elemental calcium. On the three examination days, while patients were taking PSC this test meal was mixed with 5 g PSC, while for home medication a dosage of 3 g PSC three times daily was prescribed; this supply is equivalent to 34.1 mmol citrate or 81.8 mEq bases.

Compliance with PSC medication was adequate up to 3 months (no dropouts). From this time onward patients objecting to long-term intake of PSC and those who criticized its palatibility were excluded from the study (15 dropouts). The remaining 17 patients were examined after continuous PSC medication over 6 months, and 10 of these attended the final examination (intake of PSC for more than 12 months). The laboratory examinations were coded as follows: I, before PSC ($n = 32$); II, after 3 months ($n = 32$); III after 6 months ($n = 17$); IV, 12 months ($n = 10$) of PSC treatment.

Analyses

All determinations (in capillary blood, serum, urine) were carried out using established procedures. Details of the methods used, and of crystalluria, have been reported elsewhere [13, 30].

Calculations, presentation of data, statistics

The renal phosphate threshold was read from the nomogram [35].The relative supersaturation products of urine with stone-forming substances were calculated using a computer program (EQUIL; [7]). Despite the sometimes non-Gaussian distribution, the arithmetic means ± SEM are given in the tables and figures for the sake of simplicity, except for the fractional citrate clearance (median; Fig. 2). The total variance over the observation period (time points I–IV) was estimated by the H-test (Kruskal-Wallis; [22]). If the H-test was significant, the data from examinations II and I (short-term effects) and IV and III (long- and median-term effects) were compared using the unpaired U- or *t*-test, as appropriate. This procedure was chosen to minimize the influence of the imbalance in the number of patients at the different time points. N-Cit and H-Cit were compared at each examination date. The frequency of filters with detectable crystals was examined using the Chi-square test [22].

Table 2. Citrate, calcium, and oxalate (per gram of creatinine) and pH values in daily urine, fasting urine and postprandial urine collected before treatment and after treatment for different periods

	n	Daily urine[a]				Fasting urine				Postprandial urine			
		Citrate (mg)	Calcium (mg)	Oxalate (mg)	pH	Citrate (mg)	Calcium (mg)	Oxalate (mg)	pH	Citrate (mg)	Calcium (mg)	Oxalate (mg)	pH
A. Pretreatment (I) versus 3 months treatment (II)													
N-Cit + H-Cit													
I	32	271 (25)	139 (11)	16 (1)	6.29 (0.08)	359 (40)	92 (7)	13 (1)	6.64 (0.12)	279 (25)	233 (17)	12 (1)	6.31 (0.11)
II	32	450 (27)*	104 (9)*	19 (1)	6.88 (0.12)*	467 (29)*	76 (6)	15 (1)	7.11 (0.12)*	478 (28)*	165 (13)*	14 (1)*	7.25 (0.15)*
Mean % change from I		66	–25	19	9	30	–17	15	7	71	–29	17	15
B. Treatment over 6 months (III) versus treatment for over 12 months (IV)													
N-Cit + H-Cit													
III	17	417 (34)	116 (10)	22 (2)	7.16 (0.10)	453 (39)	72 (5)	17 (2)	7.16 (0.13)	446 (33)	157 (15)	16 (1)	7.12 (0.18)
IV	10	382 (52)	141 (19)	21 (3)	6.79 (0.26)	404 (51)	86 (13)	18 (2)	6.87 (0.29)	487 (44)	215 (32)	15 (2)	6.66 (0.22)
Mean % change from III		–8	22	–5	–5	–11	19	6	–4	9	37	–6	–6
C. H-test (over I–IV)		<0.001	<0.05	<0.05	<0.001	<0.05	ns	ns	<0.01	<0.001	<0.01	<0.05	<0.001

Values shown are means (SEM); ns, not significant. See also "Materials and methods" and Table 1

[a] Upper and lower limits of normal in this laboratory: calcium <230 mg, oxalate <31 mg, citrate >200 mg (all per gram of urinary creatinine)

* $P \leq 0.05$ (comparison with value at the time point I, same protocol)

Results

Acceptance, compliance, side effects of PSC, acid-base metabolism, urinary volumes

A large number of patients rejected the long-term intake of any drug, in this case PSC. No patient reported, either spontaneously or on being questioned, undesirable side effects, such as gastrointestinal or cardiovascular complaints, that might have been caused by potassium (daily dosage of 40.9 mmol) or sodium (daily dosage of 40.9 mmol) in the PSC. Blood pressure remained unchanged with PSC (for values at time point I see Table 1). Under PSC compensated metabolic alkalosis developed, as expected; bicarbonate was already increased after 3 months' PSC (N-Cit + H-Cit $P < 0.02$, N-Cit $P < 0.01$; II versus I) and remained at this level, while the capillary pH did not change at any time point (I–IV; data not shown).

The urinary volumes (24-h, 2-h, 3-h urine) were statistically unchanged during the entire observation period (H-test; I–IV); in N-Cit and H-Cit the respective values ranged between 1.472 and 2.150, 180 and 273, 190 and 274 ml (collecting periods in the given order).

Potassium, sodium, ammonium, urea, in 24-h urine

Assuming an average excretion of 1.3 g creatinine per day and complete renal elimination of the 40.9 mmol potassium and sodium, respectively, supplied by PSC, regular intake of PSC was indicated by excretion of both electrolytes of 32 mmol over the baseline values (time point I). This was roughly the case. The mean values (mmol per g creatinine) were: potassium – N-Cit + H-Cit 36 (I), 57 (II), 63 (III), 52 (IV); N-Cit 42 (I), 60 (II), 64 (III), 52 (IV); H-Cit 30 (I), 53 (II), 62 (III), 52 (IV); sodium – N-Cit + H-Cit 122 (I), 133 (II), 166 (III), 151 (IV); N-Cit 128 (I), 123 (II), 174 (III), 156 (IV); H-Cit 115 (I), 145 (II), 160 (III), 146 (IV). It is worth noting that urinary potassium excretion was significantly raised, by a factor of 1.6, at time point II, while a mean sodium excretion approximately equal to the calculated increase (see above) was not observed until time point III (difference not significant). On the basis of these data patient compliance was judged to be adequate. As expected, ammonium tended toward lower values under medication, and after 3 months PSC ammonium was significantly decreased in H-Cit; urea was statistically unchanged (data not shown).

Citrate, calcium, oxalate, pH in 24-h 2-h, 3-h urine of the group N-Cit + H-Cit (Table 2), *magnesium*

In the 24-h urine, citrate and pH were increased after 3 months of treatment with PSC (II), and the mean oxalate was also high ($P < 0.06$); with continued medication (III, IV) citrate and pH tended toward the baseline values. Calcium was decreased after 3 months of medication (II), but exhibited pretreatment values at date IV.

Magnesium was not influenced by PSC in the 24-h, 2-h or 3-h urine (data not shown).

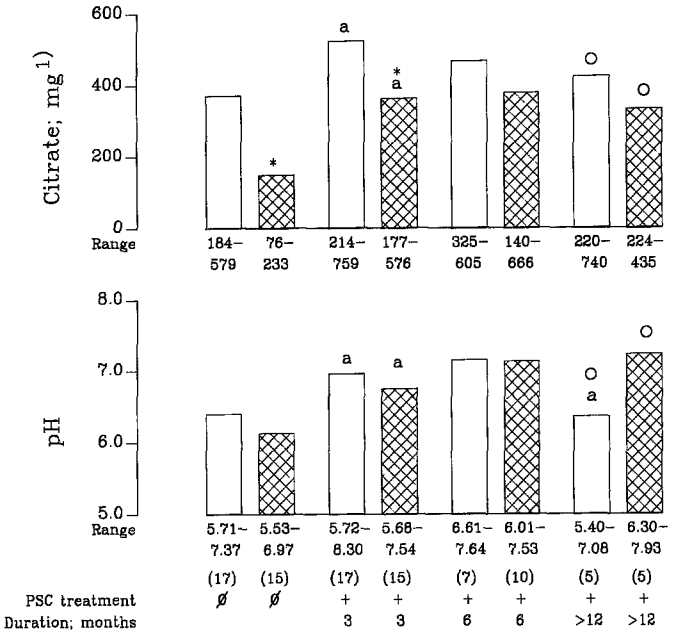

Fig. 1. Citrate and pH in 24-h urine of RCU patients. *Open columns,* patients with normocitraturia; *hatched columns,* patients with hypocitraturia. Columns represent mean values, with the range of individual values shown below; ( ), number of observations. ø; Before treatment; + PSC during medication (3, 6, > 12 months); O, $P < 0.05$ (H-test); a, $P < 0.05$ or smaller, 3 months' treatment (II) versus pre-treatment (I), and > 12 months' (IV) versus 6 months' (III) treatment, respectively, in the same group; *, $P < 0.05$ versus normocitraturia; 1) per g creatinine

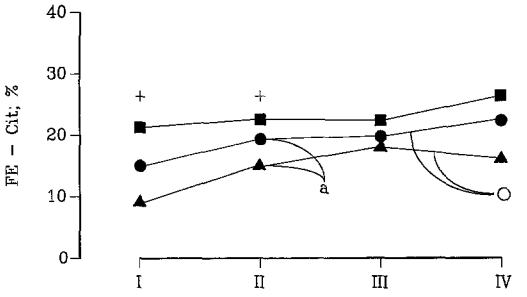

Fig. 2. Fractional citrate clearance (FE-Cit) in 2 h morning urine, after a 12- to 15-h nocturnal fasting period. Data are medians (the range of individual values is available upon request from the corresponding author); the upper limit of normal in this laboratory is 30%. ●, N-Cit + H-Cit; ■, N-Cit; ▲, H-Cit. O, $P < 0.05$ (H-test); *a*, $P < 0.05$, 3 months' PSC treatment (II) versus pretreatment (I); +, $P < 0.05$, N-Cit versus H-Cit

In 2-h-fasting urine, citrate and pH were raised after 3 months PSC, but then tended toward baseline values. Calcium and oxalate remained unchanged.

In 3-h postprandial urine, i.e. after ingestion of the test meal together with PSC, citrate, oxalate and pH were increased at examination date II and calcium was decreased. After more than 12 months PSC (IV) calcium was as low as at examination date I, and the pH also tended toward the baseline values.

Citrate, pH (Fig. 1), *calcium, oxalate in 24-h urine of subgroups N-Cit and H-Cit*

After 3 months PSC (II), citrate and pH were increased in both groups. However, in N-Cit the pH was decreased at date IV as compared with date III. Direct comparison showed that the mean citrate was always lower in the H-Cit than in the N-Cit subgroup, despite continuous medication. It should be noted, however, that the differences between the two subgroups existing prior to treatment was virtually eliminated by PSC. In contrast, with continuous medication the pH in H-Cit tended toward higher values than in N-Cit.

In both subgroups calcium remained unchanged by PSC; the values for mean excretion (mg per g creatinine) were: N-Cit – 132 (I), 108 (II), 109 (III), 139 (IV); H-Cit – 148 (I), 100 (II), 122 (III), 144 (IV). Oxalate tended toward higher values in N-Cit, and was significantly elevated ($P < 0.01$) in H-Cit, maintaining a high level during long-term medication; the mean values (mg per g creatinine) were: N-Cit 18 (I), 18 (II), 22 (III), 20 (IV); H-Cit – 14 (I), 20 (II), 23 (III), 21 (IV). Direct comparison at each examination date revealed only insignificant differences in calcium and oxalate in N-Cit and H-Cit.

Citrate in fasting blood, creatinine clearance, citrate clearance (data not shown), fractional citrate clearance (Fig. 2) *in 2-h fasting urine*

Serum citrate and creatinine clearance remained statistically unchanged during PSC, but revealed some tendency toward low values. After 3 months treatment with PSC, citrate clearance and fractional citrate clearance were significantly increased in N-Cit + H-Cit, as well as in H-Cit (Fig. 2). On average, these two parameters were always higher in N-Cit than in H-Cit (I–IV), and at time points I and II the differences were significant.

Supersaturation (Fig. 3) *and crystalluria in 3-h postprandial urine*

After 3 months treatment with PSC (II), hydroxyapatite supersaturation was increased in all groups, and also at date III was still at the high level of date II; after more than 12 months PSC (IV), in N-Cit + H-Cit and H-Cit, hydroxyapatite supersaturation was decreased compared with date III. In contrast, the supersaturation of brushite or calcium oxalate was not altered.

It is worth noting that in H-Cit the mean supersaturation of the three stone-forming substances (HAP, BRU, CaOx; Fig. 3) was higher than in N-Cit at each examination, with the exception of HAP at date II and CaOx at date IV. With respect to brushite supersaturation the difference was significant at date I, with respect to calcium oxalate at date II.

The score of the various crystalluria phases (isotropic, spheroids, uric; for details see [13]), and also the number of filters with detectable crystals, did not change under PSC (data not shown). The mean score of the isotropic phase – which is identical with amorphous calcium phosphate [13] – increased; this increase roughly paral-

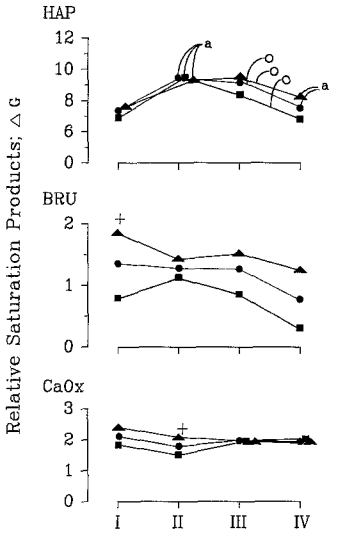

Fig. 3. Relative supersaturation products of hydroxyapatite (HAP), brushite (BRU), calcium oxalate (CaOx), in 3-h postprandial urine. Data are mean values (standard deviations are available upon request from the corresponding author). The upper limits of normal in this laboratory are: hydroxyapatite < 7.7, brushite < 0.9, calcium oxalate < 3.8. ●, N-Cit + H-Cit; ■, N-Cit; ▲, H-Cit. ○, $P < 0.05$ (H-test); *a*, $P < 0.05$, 3 months treatment (II) versus pretreatment (I), and > 12 months' (IV) versus 6 months' (III) treatment, respectively; +, $P < 0.05$ N-Cit versus H-Cit

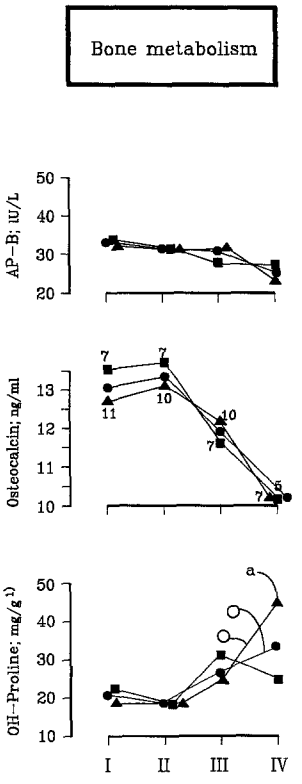

Fig. 4. Data on bone metabolism. Bone alkaline phosphate (AP-B) and osteocalcin in fasting serum, excretion of hydroxyproline (OH-proline) in 24-h urine. Data are mean values at examination points I–IV (standard deviations are available upon request from the corresponding author). Upper limits of normal in this laboratory: AP-B < 65, osteocalcin < 12, hydroxyproline < 47 (units as in the figure). ●, N-Cit + H-Cit; ■, N-Cit; ▲, H-Cit. For numbers of patients per group see Materials and methods, except for osteocalcin (see Arabic numbers). ○, $P < 0.05$ (H-test); a, $P < 0.05$ for > 12 months' (IV) versus 6 months' (III) treatment; [1] creatinine

leled the rise in the hydroxyapatite supersaturation (Fig. 3). It should be noted that the urinary pH also increased until date III, and that the pH is a determinant of calcium phosphate supersaturation [7] and calcium phosphate crystalluria [1].

Parathyroid gland function, bone metabolism (data for bone alkaline phosphate, osteocalcin, hydroxyproline see Fig. 4)

In the overall RCU group, and in the two subgroups, serum total calcium, parathyroid hormone, renal phosphate threshold and urinary cyclic AMP – all indicators of parathyroid gland function – as well as serum alkaline phosphate (total, isoenzyme) and osteocalcin – all indicators of bone metabolism [8, 9, 15] – remained at comparable levels under PSC. Hydroxyproline, another indicator of bone metabolism [8, 9, 15], was elevated by PSC in N-Cit + H-Cit and in H-Cit; this PSC effect was significant in H-Cit at date IV. Between N-Cit and H-Cit there were no significant differences with respect to these variables.

An approximately concordant increase in osteocalcin and hydroxyproline, and within limits also in alkaline bone phosphatase, would be characteristic of an increased bone turnover. However, such a constellation was lacking (see Fig. 4). Under PSC these parameters dissociated, i.e. osteocalcin and bone phosphatase tended toward low, hydroxyproline toward high values, in analogy to our previous observation on the effects of PC [30]. It should be noted that, with respect to osteocalcin, the number of patients was small (see arabic numbers, Fig. 4).

Discussion

PSC is used in the metaphylaxis of RCU because it elevates urinary citrate and pH [28, this study]. It is generally assumed that owing to these changes stone formation occurs less frequently. So far, the question remains as to whether these PSC effects were maintained over the long term, and also whether additional effects have developed. Evidence for the latter has been provided by an identically organized study on PC [30].

Response of RCU as a whole group (N-Cit + H-Cit) to PSC

Our knowledge about the mechanisms underlying the PSC-induced increase in citraturia and pH is limited. The state of acid-base metabolism is considered the most important determinant of urinary citrate [11], while increased citrate supply to renal glomeruli does not necessarily result in hypercitraturia [2]. In the organism, oral alkali citrate is degraded to buffer bases, with 3 mmol bicarbonate resulting from 1 mmol triply charged citrate. Accordingly, after 3 months of treatment with PSC, compensated metabolic alkalosis – to which increased

citraturia could be ascribed [11, 31] – was observed (Results). Despite the tendency toward metabolic alkalosis, serum citrate and fractional citrate clearance remained unchanged over the entire observation period (Fig. 2). Since the two parameters were assessed under conditions of fasting, they may not allow sufficient characterization of postprandial renal handling of citrate under PSC. Unfortunately, in the present study, repeat blood sampling was not performed in the postprandial period directly preceded by intake of PSC together with the test meal, so that assessment of postprandial renal citrate handling was not possible.

The progressive decline toward baseline values of citraturia and urinary pH under long-term PSC medication was unexpected. With respect to pH, a similar impression was given by the study on PC [30], which revealed declining values in the presence of maintained high citrate. Thus, the phenomenon appears to be characteristic for exogenous citrate, possibly potassium citrate, whereas the contribution of sodium, as contained in PSC, to citraturia is uncertain. It may be speculated that with long-term intake of alkali citrates some attenuation in the responsiveness of processes controlling acid-base and citrate homeostasis may develop. However, a different influence of PC and PSC can be seen regarding ammonia and urea, both components of acid-base metabolism [10]: while PC decreased urinary ammonia and increased urinary urea [30], PSC, in the present work, was virtually ineffective.

When treating RCU with alkali citrates, a permanent increase in the stone inhibitor citrate and a permanent reduction in the stone promotor calcium would be the ideal combination of effects. The reality, however, appears to be somewhat different. As with PC [30], the decrease in urinary calcium was restricted to short-term PSC medication. A possible explanation may be insufficient intra-intestinal complexation of calcium by citrate, resulting in de-inhibition of net intestinal calcium absorption between time points II and IV (Table 2). For inhibition of calcium absorption was found in acute experiments, with prevalence of calcium: citrate molar ratios lower than 2.1 in the gut lumen [20, 21]. Militating against this would be the continuous increase in oxaluria, which is considered to be a result of effective calcium ion binding by a number of agents, including citrate. Also, metabolic alkalosis-induced enhanced renal tubular calcium reabsorption has been documented [34]. Alternatively, therefore, the return to baseline values of urinary calcium and pH at the time points II–IV may have reflected an attenuation of the alkalinizing effect of PSC. This assumption appears all the more valid, since PSC proved to be an anticalciuretic agent at time point II; despite the calciuretic action of its sodium moiety. It is noteworthy that PC, which is devoid of sodium, also did not prevent the reincrease in urinary calcium [30].

We reported an increasing frequency of amorphous calcium phosphate in the urine following 3 months of PSC medication in RCU [28]. This observation was associated with increased supersaturation of urine with hydroxyapatite. In the study on PC [30] and in the present one on PSC, the urine contained only insignificantly more amorphous calcium phosphate particles, and this situation was accompanied by a concordant pattern of pH and hydroxyapatite supersaturation (Fig. 3). Despite the favorable thermodynamic environment, the transition to mature hydroxyapatite crystals was probably prevented by the higher levels in the urine of the crystallization inhibitor citrate [12].

Possibly associated with RCU is an osteopathy of as yet unclarified etiology [27, 33]. As in our previous work on PC [30], in the present study on PSC we observed opposite developments of bone alkaline phosphatase, osteocalcin on the one hand, and hydroxyproline on the other, although all are considered indicators of bone turnover [8, 9, 15]. A change in parathyroid gland function cannot be considered the cause (Results). Elevated serum levels of 1,25-dihydroxyvitamin D have been documented in many RCU patients [29], and this D metabolite enhances bone resorption via stimulation of osteoclasts [32]; in addition, the solubility of bone mineral in vitro is accelerated by high citrate concentrations [19]. Serum citrate in RCU is not low, but normal or even higher than normal [26]. Thus it is tempting to speculate that in untreated RCU, bone, the body's greatest citrate reservoir [19], is citrate-deficient due to a blockage of citrate influx, and that bone may act as a sink for exogenous citrate supplied in large amounts with the medication. Pak [18] reported improved bone mineral content in RCU patients who had undergone PC treatment. In the absence of data on the state of bone mineral it remains uncertain whether the low bone alkaline phosphatase, low osteocalcin, and high hydroxyproline observed in the present and the previous [30] work are sequelae of administration of (potassium-containing) citrate, or of bases, or result from some combination of these, and whether this spectrum of events reflects a beneficial development of bone metabolism. Complementary studies with neutral sodium citrate appears desirable.

Peculiarities of the H-Cit subgroup during medication

The details of the pathophysiology of hypocitraturia in RCU are unknown [14, 24]. Therefore, a separate consideration of two subgroups showing either normal or low citrate in the daily urine at entry on the study would appear reasonable, since it allows us to identify differences in responsiveness to PSC. In fact, throughout the entire course of medication, urinary citrate excretion in H-Cit remained lower than that seen in N-Cit. Conversely, also in H-Cit, urinary pH tended toward higher values than in N-Cit after 6 months PSC (Fig. 1), and the same holds for the supersaturation products of crystal- and stone-forming substances (Fig. 3). On the basis of our present knowledge we are unable to provide a plausible explanation for this different behavior.

Concluding remarks

From the present data it would appear that PSC induces increased citraturia in RCU, but also that this effect diminishes with duration of medication. The time period which may be critical for the development of the undesired counterregulation of citraturia is approximately 6 months (for urinary calcium and pH see above). These facts may

warrant a revision of present therapeutic schedules with alkali citrate involving the intake of a fixed dose per day, in favor of long-term medication interrupted by treatment-free intervals. While we were unable to elicit negative influences that could be ascribed to the sodium component of PSC, for example on blood pressure, we were able to show some as yet unknown modulation of the metabolism of extrarenal organs. We are still unaware of the underlying causes of this.

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