Cross-over study of the influence of bicarbonate-rich mineral water on urinary composition in comparison with sodium potassium citrate in healthy male subjects

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Urine volume is the greatest risk factor for nephrolithiasis. High fluid intake is the first general advice given to stone-forming patients for the prevention of their recurrence. The aim of the present study was to evaluate the influence of bicarbonate-rich mineral water (1715 mg bicarbonate/l) on urinary-stone risk factors in comparison with sodium potassium citrate, a well-established treatment for urinary stones. The mineral water and sodium potassium citrate were administered in equimolar concentrations, with respect to the alkali load. All investigations were carried out in healthy male subjects aged 23–38 years. The study followed a cross-over design. All subjects received a standardized diet during the cross-over phase, which was formulated according to the dietary recommendations of the German Society of Nutrition (Deutsche Gesellschaft für Ernährung, 1996). On the loading day of the cross-over phase, fruit tea was substituted for either mineral water or sodium potassium citrate dissolved in fruit tea. The treatment offered during the second part of the cross-over phase was continued for a 4-week follow-up under normal dietary conditions. During the cross-over phase, there was a significant increase in urinary pH ($P < 0{\cdot}001$). There was also a significant increase in the excretion of citric acid ($P < 0{\cdot}01$), a decrease in the excretion of oxalic acid, and therefore a decrease in the relative supersaturations for calcium oxalate and uric acid. In the follow-up phase also, the relative supersaturations decreased and there were beneficial effects on the other urinary variables. The effect of the bicarbonate-rich mineral water was similar to that of the sodium potassium citrate, which suggests that it could be useful in the prevention of the recurrence of calcium oxalate and uric acid stones.

Mineral water: Calcium oxalate: Uric acid

The most common urinary calculi in affluent societies have either calcium oxalate or uric acid as the main component; in Germany, about 70 % of urinary stones consist mainly of calcium oxalate and approximately 10 % consist mainly of uric acid (Trinchieri, 1996; Hesse & Siener, 1997).

Although urolithiasis is a multifactorial disease, fluid intake is one of the most important factors involved. A high fluid intake is therefore the first general advice given to stone-forming patients to prevent their recurrence (Pak *et al.* 1980; Borghi *et al.* 1996). Fluid intake has two major consequences. First, it has a diluting effect; by increasing urine output, the concentration of constituent ions and the saturation of stone-forming salts are lowered. Second, fluid composition has a direct influence on urine composition and crystal formation (Hesse *et al.* 1993). Several fluids have been found to be suitable, including mineral water (Hesse *et al.* 1993; Borghi *et al.* 1996; Rodgers, 1997), orange juice (Hesse *et al.* 1993; Wabner & Pak, 1993), apple juice, and fruit and herbal teas (Vahlensieck, 1986). Care should be taken to avoid fluids containing lithogenic agents which may increase the risk of stone formation. Coffee, black tea, alcohol (Vahlensieck, 1986) and cola (Weiss *et al.* 1992; Rodgers, 1999) are lithogenic agents. In the metaphylaxis and therapy of calcium oxalate urolithiasis it is beneficial to decrease the excretion of lithogenic agents such as Ca, oxalate and urate, but to increase the excretion of Mg and citrate which have powerful inhibitory effects (Consensus Conference, 1988; Tiselius, 1997). Citrate chelates Ca in solution forming a highly-soluble Ca–citrate complex that decreases the ionic concentration

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Table 1. Composition of the standardized daily diet fed to healthy male subjects during the cross-over phase of the study*

Food item	Amount (g)	
Breakfast		
Bread rolls	100	
Butter	20	
Jam	25	
Quark cheese, fresh (20 % fat in DM)	125	
Snack		
Fruit yoghurt (3·5 % fat)	150	
Apple	150	
Lunch		
Beef	60	
Gravy	120	
Vegetables, mixed (carrots, peas, viper's grass (*Scorzonera hispanica*), cauliflower)	120	
Pasta	120	
Snack		
Fruit yoghurt (3·5 % fat)	150	
Wholemeal biscuit bar	25	
Dinner		
Rye and wheat bread	50	
Rye wholemeal bread	75	
Butter	20	
Sausage	30	
Ham, cooked	30	
Cheese, fresh (60 % fat in DM)	17	
Tomato	50	
Snack		
Crispbread	10	
Butter	10	
Salami	25	
Banana	150	
Beverages		
Coffee	200 ml	
Milk (3·5 % fat)	50 ml	
Fruit tea†	2000 ml	
	Adaptation period	Loading period
Composition		
Energy: MJ	10·612	10·612
kcal	2533	2533
Protein (g)	96	96
Fat (g)	107	107
Carbohydrate (g)	290	290
Ca (mg)	853	1041
Mg (mg)	282	386

* For details of the study protocol, see Table 2 and p. 867.

† During the loading period of the cross-over test phase, the fruit tea was substituted with either sodium potassium citrate dissolved in fruit tea or with bicarbonate-rich mineral water. The fruit tea has no influence on urinary composition (T Keßler and A Hesse, unpublished results).

of Ca (Parivar *et al.* 1996). Uric acid can be held in solution, and stones composed of uric acid can be dissolved by increasing the urinary pH to at least 6·5 (Hesse *et al.* 1997).

In the medical treatment of calcium oxalate and uric acid stone formation, alkaline salts of citrate and bicarbonate have been used to make the urine more alkaline (Sakhaee *et al.* 1983) and thus increase citric acid excretion. Metabolism of citrate induces a metabolic alkalosis, which causes an increase in cytoplasmic pH and bicarbonate, thus making the urine more alkaline and decreasing the mitochondrial pH gradient. This process inhibits the tricarboxylate carrier, slowing entry of citrate into the mitochondria. The citrate level in the cytoplasm increases, tubular citrate reabsorption is reduced, and citrate excretion increases. The opposite changes occur during metabolic acidosis (Simpson, 1983).

The aim of the present study was to evaluate the influence of a bicarbonate-rich mineral water on several urinary stone risk factors, and to compare mineral water with sodium potassium citrate, a well-established treatment for calcium oxalate and uric acid stones. The two treatments were administered in equimolar concentrations with respect to the alkali load.

Materials and methods

The study protocol was approved by the Ethical Committee of the Faculty of Medicine, University of Bonn, Germany.

All investigations were carried out using twenty-four healthy male subjects with no previous history of urinary calculi or other renal disorders. The mean age was 29·2 (range 23–38) years. In a pre-phase, before the cross-over phase, each subject was required to provide two 24 h urine

Table 2. Study protocol

(a) Pre-phase				
2 × 24 h urine collection; blood sample; ECG				
No treatment				
(b) Cross-over phase				
Standardized diet*				
Repeat days 1–5 (swap treatment)				
Adaptation period:			Loading period:	
Day 1	Day 2	Day 3	Day 4	Day 5
24 h urine collection			3 h urine fractions	24 h urine collection
No treatment			Group A (*n* 12): NaK citrate Group B (*n* 12): Mineral water	
(c) Follow-up phase				
Week 1	Week 2	Week 3	Week 4	
Normal dietary conditions 24 h urine collection (weekly) Treatment as for second 5 d period of cross-over phase				

ECG, electrocardiogram.
* For details of diet, see Table 1.

collections under normal dietary conditions (for details of urinary analysis, see p. 867). In addition, an electrocardiogram was carried out and a blood sample was collected. Glutamate-pyruvate transaminase, γ-glutamyl transpeptidase, creatinine and the numbers of leucocytes and platelets were determined in serum. Subjects with values outside the reference range were excluded from the study.

The present study followed a cross-over design. Each subject was randomly assigned to one method of treatment, sodium potassium citrate or bicarbonate-rich mineral water. All subjects received a standardized diet (Table 1) formulated according to the dietary recommendations of the German Society of Nutrition (Deutsche Gesellschaft für Ernährung, 1996). The diet consisted of normal food items to ensure consistency of the investigation results. The subjects were required to eat all the food offered, and the same type and amount of food was consumed every day. The study protocol is summarized in Table 2. The cross-over phase was divided into two consecutive periods of 5 d each. A 3 d adaptation period on the standardized diet without any treatment preceded each loading period. Day 3 was chosen as the control day for loading day 5. On loading days 4 and 5, a neutral fruit tea with no influence on the urinary composition (T Keßler and A Hesse, unpublished results) was substituted with the mineral water or sodium potassium citrate dissolved in fruit tea and 500 ml was given at 11.00, 14.00, 17.00 and 20.00 hours. Urine samples (24 h) were collected each day, except on day 4 when the urine was collected every 3 h. The control day for the collection of urine every 3 h (day 4) was during the pre-phase, which we carried out to determine whether the study protocol was acceptable to the subjects (not shown in Table 2). Sport and other extreme exercise were not permitted during the cross-over phase. Subsequent to the cross-over phase, a follow-up over 4 weeks was undertaken when subjects returned to their normal diets but continued to receive the same form of treatment as the second week of the cross-over phase, on a daily basis. Once weekly a 24 h urine collection was made. The second 24 h urine collection of the pre-phase period acted as control.

The bicarbonate-rich mineral water (Staatl. Fachingen; Fachingen Heil- u. Mineralbrunnen GmbH, Mainz, Germany) had the following composition (mmol/l and mg/l respectively): pH 6·12, Na 21·97, 505; K 0·3325, 13·0; Ca 2·36, 94·0; Mg 2·14, 52·0; bicarbonate 28·1, 1715; sulfate 0·30, 29·0. Sodium potassium citrate dihydrate (Oxalyt®C; Madaus AG, Köln, Germany) contained (mmol/3 g granules): citrate 10·9, Na 13·1, K 13·1. Equimolar concentrations with respect to the alkali load were achieved by a daily treatment dose of 2000 ml mineral water of 2·55 g sodium potassium citrate granules.

The urine was collected in polyethylene containers and mixed with 5 ml/l of a 5% solution of thymol in isopropanol to preserve the urine. During the collection period, the containers and their contents were maintained at 5°C. Urine samples were tested for the presence of blood and infection. Nitrite-positive and haematuria samples were discarded. In addition, volume, specific gravity (urinometer) and pH (potentiometer) were recorded. The methods used in the analysis of urine samples, with the relative CV for each method were as follows: Na, K and Ca by flame photometry, 1·3; Mg by xylidyl-blue reaction, 0·3; NH_4^+ by ion-selective electrode, 1·5; Cl^- by coulomb metric titration, 2·0; inorganic phosphate by phosphate molybdate reaction, <5; inorganic sulfate by nephelometry, <5; creatinine by Jaffé reaction, 2·0; uric acid by uricase method, <5; citric acid by citrate lyase method, 1·6; oxalic acid by HPLC–enzyme reactor method (Hönow *et al.* 1997), 0·5 (Hesse & Bach, 1982; Hesse *et al.* 1997).

The relative supersaturation values for calcium oxalate, uric acid and brushite were calculated using Equil 2 (Finlayson, 1977; Werness *et al.* 1985). The Wilcoxon matched-pairs signed-rank test, as a non-parametric test of significance, was used for testing two matched samples (control and loading day). $P < 0{\cdot}05$ was considered to be statistically significant.

Results

The main results of the 24 h urine samples from the cross-over phase are reported in Table 3. There were significant increases in pH ($P < 0{\cdot}001$) and in the excretion of citric acid ($P < 0{\cdot}01$) for both treatments. Significantly decreases were also found in the excretion of oxalic acid for both mineral water ($P < 0{\cdot}001$) and sodium potassium citrate ($P < 0{\cdot}05$). Decreases in the excretion of Ca and uric acid were only significant in the sodium potassium citrate group ($P < 0{\cdot}05$ for uric acid and $P < 0{\cdot}01$ for Ca). On the basis of the altered urinary composition we calculated significant decreases in the relative supersaturations for calcium oxalate ($P < 0{\cdot}001$ for mineral water and $P < 0{\cdot}01$ for sodium potassium citrate) and uric acid ($P < 0{\cdot}001$ for both treatments). An increase was observed in the relative supersaturation for brushite although this was not significant. There were no significant differences between the treatments for either control (day 3) or loading (day 5) days.

The decreases in the relative supersaturation of calcium oxalate (Fig. 1 and Table 4) and uric acid (Fig. 2 and Table 5) can also be seen in the circadian rhythm of urinary excretion. The values for the 3 h urinary collections for the sodium

Table 3. Urinary variables measured in 24 h samples from healthy male subjects on a standardized diet before and after loading with either bicarbonate-rich mineral water or sodium potassium citrate during the cross-over phase of the study†

(Mean values with their standard errors)

	Mineral water (*n* 24)				Sodium potassium citrate (*n* 23)			
	Control‡		Load		Control‡		Load	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Volume (l)	2·02	0·10	2·30*	0·11	2·08	0·10	2·18	0·11
pH	6·06	0·07	6·68***	0·07	6·05	0·07	6·60***	0·06
Ca (mmol/d)	4·95	0·48	4·31	0·33	4·85	0·42	4·08**	0·35
Mg (mmol/d)	5·21	0·22	4·70	0·34	5·12	0·17	4·69	0·33
Oxalic acid (mmol/d)	0·254	0·02	0·189***	0·02	0·226	0·01	0·203*	0·01
Citric acid (mmol/d)	2·677	0·18	3·103**	0·22	2·817	0·21	3·281**	0·24
Uric acid (mmol/d)	3·73	0·18	3·48	0·15	4·00	0·13	3·42*	0·17
RS: Calcium oxalate	3·03	0·33	1·81***	0·23	2·80	0·37	2·10**	0·37
Uric acid	1·43	0·25	0·38***	0·08	1·53	0·22	0·41***	0·07
Brushite	0·85	0·16	0·93	0·10	0·85	0·14	0·92	0·10

RS, relative supersaturation.
Mean values were significantly different from those for the control: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.
† For details of diet and procedures, see Tables 1 and 2 and pp. 866–867.
‡ Values measured on day 3 of the cross-over phase.

potassium citrate and the mineral water treatments were much lower than those for the treatment-free control day.

The main results of the follow-up phase are shown in Table 5. Under normal dietary conditions, there were significant favourable changes in pH value (mineral water: weeks 1, 2 and 4 $P < 0·01$, week 3 $P < 0·05$; sodium potassium citrate: weeks 1 and 3 $P < 0·01$, week 2 $P < 0·05$) and a higher excretion of citric acid in both groups; significant ($P < 0·05$ for weeks and 2 and 4) in the mineral water group. With the exception of one measurement period (week 4 for mineral water), the excretion of oxalic acid was lower than that on the control day; the differences were significant ($P < 0·05$) for weeks 2 and 3 in the mineral water group and for week 3 in the sodium potassium citrate group. The changes in the urinary variables resulted in beneficial changes in the relative supersaturations of calcium oxalate and uric acid (Table 5). The excretion of Ca, Mg and uric acid showed very small changes. With the exception of urinary volume, which was significantly higher in the mineral-water group (weeks 1, 2 and 3 $P < 0·001$ and week 4 $P < 0·05$), there were no significant differences between the mineral-water and sodium potassium citrate groups for any of the measurement periods.

Discussion

The beneficial effects in relation to the risk of calcium

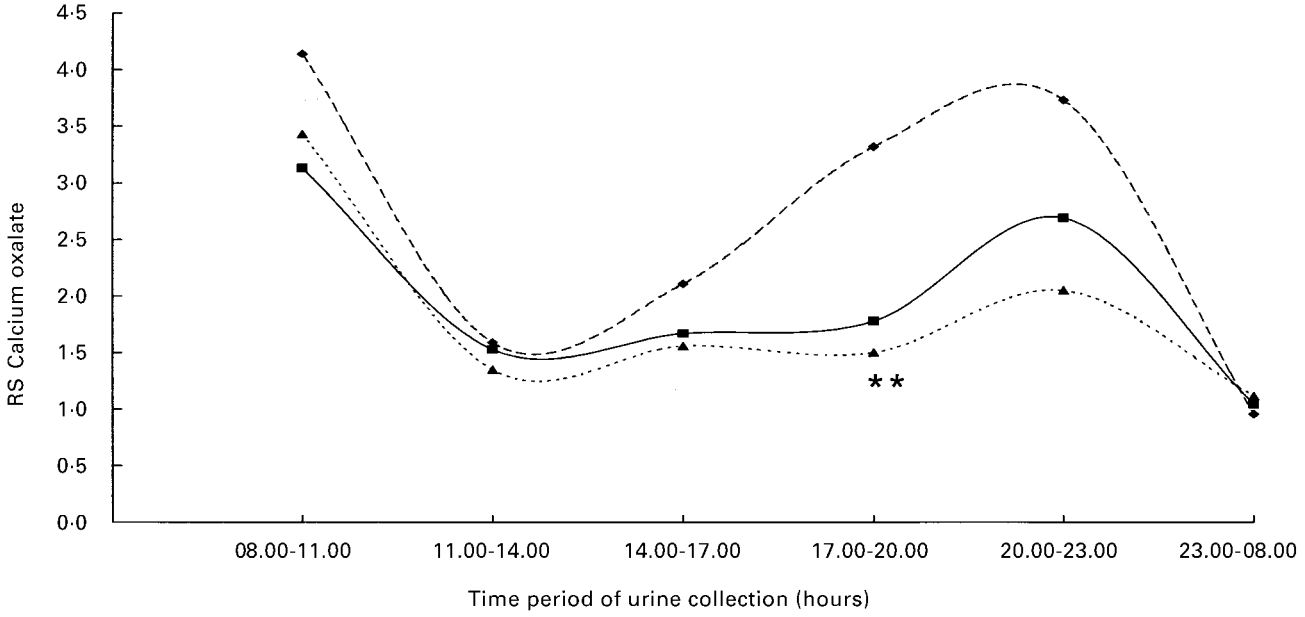

Fig. 1. Circadian rhythm of the relative supersaturation (RS) for calcium oxalate in 3 h collections of urine (for the final collection, over 9 h, the value was divided by 3) from healthy male subjects on a standardized diet receiving bicarbonate-rich mineral water (▲) or sodium potassium citrate (■) in the cross-over phase, or a neutral fruit tea (control) in the pre-phase (◆). For details of procedures, see Table 2 and p. 867. Values are means for twenty-four subjects taken from Table 4. Mean values were significantly different from the control values: **$P < 0·01$.

Table 4. Circadian rhythm of the relative supersaturation for calcium oxalate and uric acid in 3 h collections of urine from healthy male subjects on a standardized diet after a load of bicarbonate-rich mineral water or sodium potassium citrate (during cross-over phase), or after a neutral fruit tea (control; during pre-phase)†

(Values are means with their standard errors for twenty-four subjects)

Collection period (hours)…	08.00–11.00	11.00–14.00	14.00–17.00	17.00–20.00	20.00–23.00	23.00–08.00
Calcium oxalate						
Mineral water: Mean	3·43	1·35	1·56	1·50**	2·05	1·12
SE	0·43	0·25	0·27	0·24	0·44	0·54
Sodium potassium citrate: Mean	3·13	1·53	1·67	1·78	2·69	1·04
SE	0·35	0·29	0·32	0·36	0·49	0·52
Control: Mean	4·14	1·59	2·11	3·32	3·73	0·96
SE	0·93	0·34	0·28	0·69	1·02	0·79
Uric acid						
Mineral water: Mean	1·70	0·48**	0·74	0·88*	0·48**	0·39***
SE	0·33	0·21	0·31	0·36	0·19	0·29
Sodium potassium citrate: Mean	1·64	0·58**	0·67	0·67*	0·67*	0·45**
SE	0·33	0·20	0·19	0·19	0·15	0·26
Control: Mean	2·42	1·39	0·83	1·87	1·93	0·88
SE	0·44	0·30	0·22	0·46	0·43	0·39

Mean values were significantly different from control values: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.
† For details of procedures, see Table 2 and p. 867.

oxalate and uric acid stone formation were due to the high content of bicarbonate in the mineral water; the consumption of Ca and Mg, and the citrate level in this treatment also contributed. The presence of bicarbonate and the metabolism of citrate leads to an increase in urinary pH, with a consequent increase in citric acid excretion. The decrease in oxalic acid excretion observed in the cross-over and follow-up phases is of particular importance, as it considerably reduces the risk of calcium oxalate stone formation. This decrease may be due to the intestinal binding of oxalic acid by Ca and Mg present in the food, and especially in the mineral water (94·0 mg Ca/l, 52 mg Mg/l).

A significant decrease in Ca excretion was also observed in a comparable investigation by Sakhaee *et al.* (1983) in uric acid stone-forming patients. There are two reasons for the decrease in Ca excretion: (1) intestinal complexing by citric acid (with sodium potassium citrate) and oxalic acid (both treatments); (2) increased reabsorption by the kidney tubuli as a result of the inhibited excretion of parathyroid hormone caused by the alkali load. The higher levels of urinary Ca in the mineral-water group under both

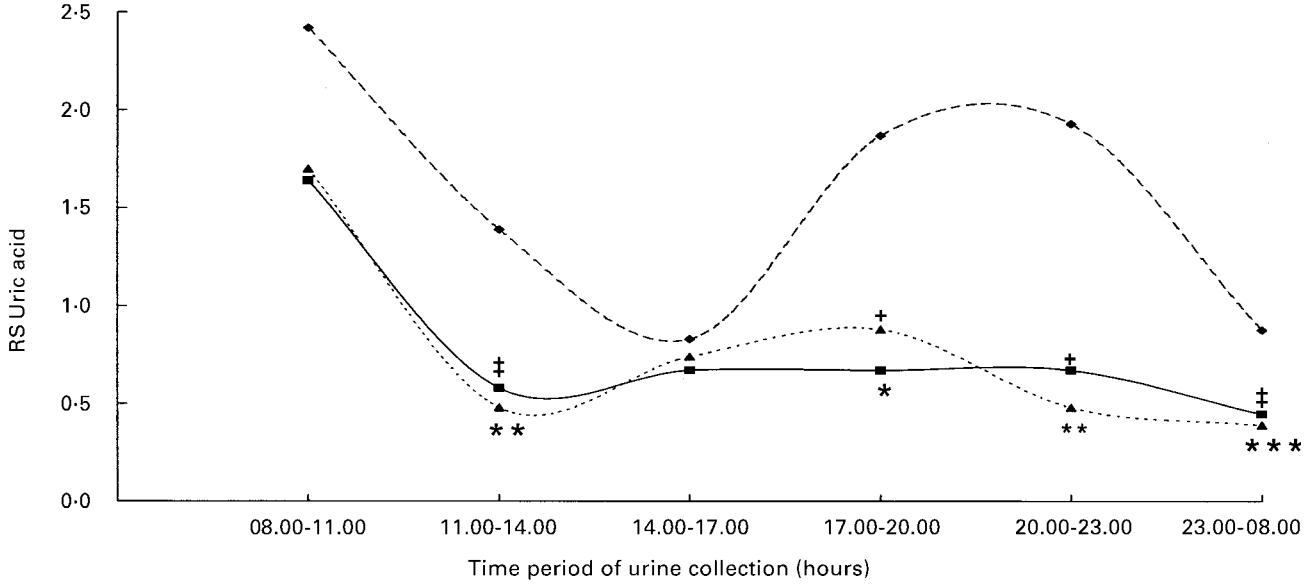

Fig. 2. Circadian rhythm of the relative supersaturation (RS) for uric acid in 3 h collections of urine (for the final collection, over 9 h, the value was divided by 3) from healthy male subjects on a standardized diet receiving either bicarbonate-rich mineral water (▲) or sodium potassium citrate (■) in the cross-over phase or a neutral fruit tea (control) in the pre-phase (◆). For details of procedures, see Table 2 and p. 867. Values are means for twenty-four subjects, taken from Table 4. Mean values for the subjects receiving mineral water were significantly different from the control values: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$. Mean values for subjects receiving sodium potassium citrate were significantly different from the control values: †$P < 0·05$, ‡$P < 0·01$.

Table 5. Urinary variables measured in 24 h samples from healthy male subjects on their normal diets receiving either bicarbonate-rich mineral water or sodium potassium citrate during the 4-week follow-up phase of the study†

(Mean values with their standard errors)

	Control‡		Week 1		Week 2		Week 3		Week 4	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Bicarbonate-rich mineral water (*n* 12)										
Volume (l)	1·86	0·15	2·28	0·17	2·80**	0·23	2·70**	0·25	2·41	0·21
pH	6·25	0·07	6·74**	0·08	6·73**	0·05	6·65*	0·09	6·77**	0·07
Ca (mmol/d)	5·03	0·87	5·05	0·78	5·39	0·81	5·13	0·73	4·87	0·68
Mg (mmol/d)	4·72	0·60	5·05	0·44	6·24*	0·87	5·80	0·83	5·48	0·61
Oxalic acid (mmol/d)	0·338	0·03	0·281	0·04	0·275*	0·02	0·275*	0·04	0·343	0·05
Citric acid (mmol/d)	2·652	0·293	3·114	0·38	3·468*	0·30	3·243	0·47	3·171*	0·30
Uric acid (mmol/d)	3·73	0·33	3·53	0·21	3·76	0·26	3·68	0·33	3·78	0·28
RS: Calcium oxalate	4·30	0·67	2·65	0·54	2·05**	0·31	2·28*	0·37	2·72	0·48
Uric acid	0·90	0·10	0·27**	0·05	0·25**	0·05	0·40*	0·19	0·27**	0·05
Brushite	0·84	0·13	1·24*	0·21	1·12	0·23	0·99	0·17	1·29*	0·19
Sodium potassium citrate (*n* 12)										
Volume (l)	1·71	0·16	1·70	0·09	1·84	0·06	1·86	0·11	1·69	0·11
pH	6·23	0·07	6·84**	0·23	6·68*	0·15	6·74**	0·13	6·55	0·17
Ca (mmol/d)	4·74	0·86	4·39	0·64	3·94	0·39	3·65	0·45	3·86	0·43
Mg (mmol/d)	5·07	0·43	5·28	0·60	4·91	0·78	5·13	0·69	5·20	0·60
Oxalic acid (mmol/d)	0·360	0·03	0·314	0·04	0·289	0·04	0·256*	0·02	0·278	0·03
Citric acid (mmol/d)	3·710	0·28	3·858	0·31	3·786	0·46	3·751	0·36	3·694	0·34
Uric acid (mmol/d)	4·33	0·27	3·91	0·32	3·63	0·30	3·88	0·29	3·36**	0·21
RS: Calcium oxalate	4·18	0·52	3·16	0·46	2·72	0·46	2·42*	0·35	3·08	0·58
Uric acid	1·41	0·28	0·65**	0·22	0·69*	0·38	0·70*	0·38	1·11	0·54
Brushite	1·13	0·31	1·50	0·28	1·20	0·19	1·23	0·232	1·27	0·21

RS, relative supersaturation.
Mean values were significantly different from those for the control: $^{*}P \leq 0{\cdot}05$, $^{**}P \leq 0{\cdot}01$.
† For details of procedures, see Table 2 and p. 867.
‡ Values measured during the pre-phase.

standardized and normal dietary conditions are due to the Ca content of the water. The lower urine flow of the sodium potassium citrate group in the follow-up phase suggests that under normal dietary conditions this group did not reach the fluid intake of the mineral-water group, which was 2000 ml/d.

The favourable increase in urinary pH and citric acid excretion has been described previously after treatment with bicarbonate-rich mineral water (Hesse *et al.* 1993) and potassium citrate (Barcelo *et al.* 1993). In the present study under both standardized and normal dietary conditions with healthy male subjects we achieved a mean daily urine pH of about 6·7 and a mean daily urinary citric acid excretion above the reference threshold of 3 mmol/d. The increased alkalinity had a beneficial effect on urinary composition; the risk of calcium oxalate and uric acid stone formation (expressed in terms of relative supersaturation) was reduced, and the risk of brushite stone formation did not increase. It is of importance that the decreases in relative supersaturation for calcium oxalate and uric acid were not only observed in the 24 h urine analyses, but were also present in the circadian rhythm. There were no concentration peaks during the day with either treatment (citrate or bicarbonate-rich mineral water).

The present study demonstrates that mineral water rich in bicarbonate (>1500 mg/l) and sodium potassium citrate in equimolar concentrations with respect to the alkali load have beneficial effects on urinary pH and the excretion of citric acid, oxalic acid and Ca, and therefore on the relative supersaturations for calcium oxalate and uric acid. At the urinary pH value observed, chemolysis of uric acid stones would be possible. Although the study was carried out on healthy subjects rather than in stone-forming patients, the findings suggest that bicarbonate-rich mineral water may be useful in preventing the recurrence calcium oxalate and uric acid stones, as well as in the treatment of hypocitraturia and/or hypercalciuria. Further research is needed to confirm this finding in stone-forming patients.

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