

## Effects of mineral composition of drinking water on risk for stone formation and bone metabolism in idiopathic calcium nephrolithiasis

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1. To assess whether the mineral content of drinking water influences both risk of stone formation and bone metabolism in idiopathic calcium nephrolithiasis, 21 patients were switched from their usual home diets to a 10 mmol calcium, low-oxalate, protein-controlled diet, supplemented with 2 l of three different types of mineral water. Drinking water added 1, 6 and 20 mmol of calcium and 0.5, 10 and 50 mmol of bicarbonate respectively to the controlled diet.

2. The three controlled study periods lasted 1 month each and were separated by a 20 day washout interval. Blood and urine chemistries, including intact parathyroid hormone, calcitriol and two markers of bone resorption, were performed at the end of each study period. The stone-forming risk was assessed by calculating urine saturation with calcium oxalate ( $\beta\text{CaOx}$ ), calcium phosphate ( $\beta\text{bsh}$ ) and uric acid ( $\beta\text{UA}$ ).

3. The addition of any mineral water produced the expected increase in urine output and was associated with similar decreases in  $\beta\text{CaOx}$  and  $\beta\text{UA}$ , whereas  $\beta\text{bsh}$  varied marginally. These equal decreases in  $\beta\text{CaOx}$ , however, resulted from peculiar changes in calcium, oxalate and citrate excretion during each study period. The increase in overall calcium intake due to different drinking water induced modest increases in calcium excretion, whereas oxalate excretion tended to decrease. The changes in oxalate excretion during any one study period compared with another were significantly related to those in calcium intake. Citrate excretion was significantly higher with the high-calcium, alkaline water.

4. Parathyroid hormone, calcitriol and markers of bone resorption increased when patients were changed from the high-calcium, alkaline to the low-calcium drinking water.

5. We suggest that overall calcium intake may be tailored by supplying calcium in drinking water. Adverse effects on bone turnover with low-calcium diets can be prevented by giving high-calcium, alkaline drinking water, and the stone-forming risk can be decreased as effectively as with low-calcium drinking water.

### INTRODUCTION

High fluid intake and urine outflow are recommended to lower the risk of stone formation in idiopathic calcium nephrolithiasis [1]. Although the resulting dilution effect involves both promoting and inhibiting substances, the overall risk of forming stones decreases through both a decrease in the urine state of saturation with calcium oxalate and calcium phosphate and an increase in the minimum supersaturation required to elicit initiation of crystallization [2]. The Tamm–Horsfall glycoprotein, the most abundant protein in human urine, changes its physicochemical properties from promoting to inhibiting by lowering ionic strength [3], as in the case of urine dilution. These beneficial effects should be amplified by supplying water of low calcium content, which would provide the maximum dilution effect associated with the minimum increase in calcium excretion.

Since hypercalciuria occurs in a considerable proportion of patients with idiopathic calcium nephrolithiasis [4], such patients are often recommended to restrict calcium intake [1, 5–8]. Calcium excretion increases in both normal and hypercalciuric subjects over a wide range of calcium intakes [9]. However, in hypercalciuric patients, calcium balance tends to be negative because the increase in urinary excretion outweighs the increase in intestinal absorption of calcium and this is often associated with enhanced bone resorption [10]. The suitability of calcium restriction has been questioned in a recent prospective study in which high dietary calcium was associated with a lower risk of developing symptomatic stones over a 4-year follow-up [11]. It has been contended that decreasing calcium content in the diet may increase intestinal absorption of

**Key words:** bone resorption, calcium nephrolithiasis, calcium oxalate, calcium phosphate, mineral water, urine state of saturation.

**Abbreviations:**  $\beta\text{bsh}$ , state of saturation with calcium hydrogen phosphate dihydrate;  $\beta\text{CaOx}$ , state of saturation with calcium oxalate monohydrate;  $\beta\text{UA}$ , state of saturation with uric acid; PTH, parathyroid hormone.

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Table 1. Chemical composition\* of the three types of mineral drinking water supplied during the study

	Low-calcium	Medium-calcium	High-calcium
pH	7.1	7.2	6.1
Calcium	0.1	3.0	10
Magnesium	0.04	1.5	1.0
Sodium	0.1	0.3	3.5
Potassium	0.1	0.1	1.2
Chloride	0.1	0.1	0.7
Sulphate	0.1	2.2	0.1
Bicarbonate	0.25	5.0	25
Carbon dioxide	0.1	2.0	47

\*In mmol/l.

oxalate and impair or cancel the beneficial effect on the risk of calcium stone formation [11, 12]. Furthermore, long-term, low-calcium diets may adversely affect bone turnover and mineral content [13].

Hence, low-calcium diets associated with low-calcium drinking water may fail to decrease the overall risk of stone formation, and may also produce osteopenia. The present study was aimed at evaluating whether the mineral content of drinking water could influence both risk of calcium stone formation and patterns of bone metabolism.

## METHODS AND MATERIALS

### Patients and study protocol

We enrolled 21 patients (8 males and 13 females, mean age  $48 \pm 9$  years) with idiopathic calcium nephrolithiasis who were referred to our Renal Stone Ambulatory. Renal function was normal in all. None had underlying systemic or renal disorders causing stone disease, nor urinary tract infection or new stones or renal colics during the study.

We designed an outpatient study protocol, subdivided into four phases, with biochemical investigations performed at the end of each study period. During the first phase (baseline), patients were studied while on their usual diets and habits. During the subsequent three study periods, lasting 1 month each and separated by a 20 day washout interval (controlled phases), patients were given detailed dietary prescriptions and were instructed to drink 2 l of three different types of mineral water of low, medium and high calcium content. The chemical composition of the mineral water (Table 1) shows that the increase in calcium content was paralleled by that of bicarbonate. Differences in both pH and bicarbonate content could be accounted for by differences in total free  $\text{CO}_2$ . Other constituents varied only marginally. Patients were assigned to each type of drinking water in a random fashion. The whole study was concluded within autumn or wintertime. Informed consent was obtained from all the patients and the study was authorised by the Direzione Sanitaria of the hospital.

Patients were classified as normocalciuric (12, seven females and five males) or hypercalciuric (six females and nine males), taking a calcium excretion of  $4 \text{ mg/day}^{-1} \text{ kg}^{-1}$  body weight during both unrestricted diet and low-calcium water study period as the cut-off value. Since the study design implied manipulations of calcium intake, we used this restrictive criterion to separate hypercalciuric patients in which hypercalciuria was independent of dietary calcium.

The controlled diets were designed to supply daily: calcium, 10 mmol; sodium, 150 mmol; oxalate, 1–2 mmol; protein, 1 g/kg body weight. Patients' compliance to diet was verified by computerizing the amount of dietary components through a guided diary recorded by the patients during three representative days of each study period. Urinary excretions of total nitrogen, net acid, inorganic sulphate and sodium were used as an additional check of compliance to diet with respect to whole protein, animal protein and salt respectively [14].

### Laboratory investigations

At the end of each study period the patients carried out 24 h and 2 h fasting urine collections. Blood was taken and analysed for relevant chemistries by means of routine methods, as described elsewhere [14]. Blood was also analysed for intact parathyroid hormone (PTH) using an immunochemiluminometric assay (ICMA; Magic Lite, Ciba Corning, Italy); 1,25-dihydroxyvitamin D by a RIA using the 1,25-dihydroxyvitamin D- $^3\text{H}$  RRA kit (Incstar Co, Stillwater, MN, U.S.A.) and osteocalcin by RIA using a commercial kit (Osca Test, Henning, Berlin, Germany). Bone resorption was evaluated by measuring, in fasting urine, total hydroxyproline by HPLC and the cross-linked N-telopeptide of type I collagen (NTX Osteomark kit, Ostex, Seattle, U.S.A.) [15].

### Statistical methods and calculations

The stone-forming potential was assessed by estimating the urine state of saturation with respect to calcium oxalate monohydrate ( $\beta\text{CaOx}$ ), calcium hydrogen phosphate dihydrate ( $\beta\text{bsh}$ ) and uric acid ( $\beta\text{UA}$ ) by means of a computer-based model, whereby a value of 1 denotes saturation, and more than 1 supersaturation. The procedure, which is similar to that used for serum, is detailed elsewhere [16, 17]. Net acid excretion was the sum of measured ammonium plus titratable acid minus bicarbonate excretions; total nitrogen excretion was the sum of urea, creatinine, uric acid and ammonium nitrogen. Results are means  $\pm$  SD and statistics were performed by a computer package (Statistix; NH Analytical Software, Iowa, U.S.A.). The significance of differences between study periods and between normocalciuric and hypercalciuric patients was assessed by non-parametric tests (Wilcoxon and Mann–

**Table 2. Renal function and nutritional indices assessed during each study period.** Statistical significance: <sup>a</sup> $P < 0.001$  compared with all other study periods. <sup>b</sup> $P < 0.05$  compared with all other study periods.

Study periods	Baseline	Low-calcium	Medium-calcium	High-calcium
Creatinine clearance (ml/min)	94 ± 18	104 ± 27	89 ± 19	92 ± 21
Sodium (mmol/24 h)	171 ± 63	200 ± 64	193 ± 64	200 ± 74
Potassium (mmol/24 h)	50 ± 20 <sup>a</sup>	60 ± 12	59 ± 14	64 ± 16
Sulphate (mmol/24 h)	17 ± 5.4	16.5 ± 3.9	20.8 ± 4.3	18.2 ± 4.8
Net acid (mmol/24 h)	48 ± 16.5	41.8 ± 15.7	49.6 ± 14.8	33.4 ± 13.3 <sup>b</sup>
Total nitrogen (mmol/24 h)	813 ± 154 <sup>a</sup>	720 ± 136	723 ± 172	731 ± 122

**Table 3. Changes of some urine components relevant for calcium stone-formation during the four study periods.** Statistical significance: <sup>a</sup> $P < 0.001$  compared with all other study periods. <sup>b</sup> $P < 0.01$  compared with medium-calcium. <sup>c</sup> $P < 0.01$  compared with all other study periods. <sup>d</sup> $P < 0.05$  compared with all other study periods.

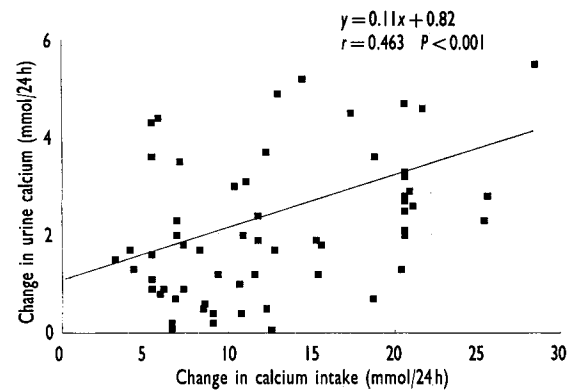
Study periods	Baseline	Low-calcium	Medium-calcium	High-calcium
Urine volume (ml/24 h)	1750 ± 441 <sup>a</sup>	2418 ± 501	2643 ± 565	2628 ± 457
pH	6.24 ± 0.53	6.44 ± 0.51	6.17 ± 0.52	6.67 ± 0.54 <sup>b</sup>
Calcium (mmol/24 h)	6.3 ± 2.9	4.8 ± 2.1 <sup>a</sup>	6.7 ± 3.2	7.8 ± 3.0 <sup>b</sup>
Phosphate (mmol/24 h)	21.6 ± 3.4	19.5 ± 4.7	20.3 ± 6.3	17.2 ± 7.6 <sup>d</sup>
Oxalate (mmol/24 h)	0.42 ± 0.13	0.46 ± 0.17	0.41 ± 0.13	0.36 ± 0.12 <sup>c</sup>
Uric acid (mmol/24 h)	4.8 ± 0.93	4.0 ± 1.1	4.3 ± 1.2	4.3 ± 1.2
Magnesium (mmol/24 h)	2.9 ± 1.04	3.3 ± 0.8	4.3 ± 1.2	5.5 ± 2.7 <sup>c</sup>
Citrate (mmol/24 h)	3.0 ± 1.6	2.9 ± 1.1	2.9 ± 1.3	3.6 ± 1.6 <sup>c</sup>

Whitney test, respectively). Conversely, correlations between two variables were set by means of Spearman's rank test.

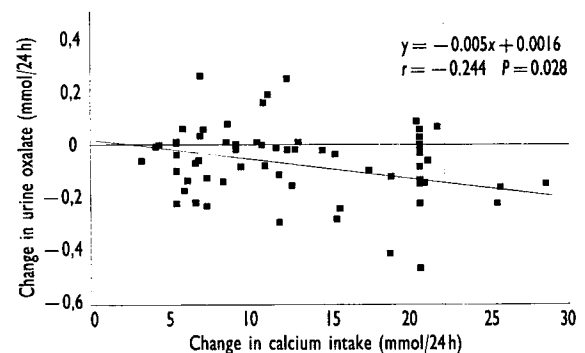
## RESULTS

As deduced from the dietary records, most of the patients had to change their current home diets after entering the study to conform to the given prescriptions. Specifically, they reduced dietary intakes of calcium and proteins by 50% and 15% respectively. Table 2 gives results of urine chemistries which can be used to check patient compliance: these indicate that patients did not modify the diet during the three controlled phases of the study, as per our instructions. Therefore, virtually all the differences in urine chemistries between study periods should be due to differences in composition of the drinking water. The diets added approximately 1, 6 and 20 mmol of calcium and 0.5, 10 and 50 mmol of bicarbonate per day to the dietary intakes during low-, medium- and high-calcium study periods respectively.

These differences in mineral intakes produced significant differences in urine chemistries relevant for stone formation (Table 3). As expected, urine volume increased with all types of water supplied. Calcium excretion with low-calcium water was lower than baseline, and increased progressively with the increase in the calcium content of drinking water. There was a significant relationship between molar differences in calcium intake and urinary calcium excretion between study periods (Fig. 1). The higher the calcium excretion the lower the oxalate excretion. The changes in oxalate excretion



**Fig. 1. Relationship between changes in overall dietary calcium and changes in urinary calcium over the three controlled study periods.**



**Fig. 2. Relationship between changes in overall calcium intake and changes in urinary oxalate over the three controlled study periods.**

during any one study period compared with another were significantly related to those in calcium intake (Fig. 2). Magnesium excretion tended to increase during the three controlled diets, and was signifi-

**Table 4. Changes of urine state of saturation with respect to calcium oxalate ( $\beta$ CaOx), calcium hydrogen phosphate dihydrate ( $\beta$ bsh) and uric acid ( $\beta$ UA) during each study period. Statistical significance: <sup>a</sup> $P < 0.001$  compared with all other study periods.**

Study periods	Baseline	Low-calcium	Medium-calcium	High-calcium
$\beta$ CaOx	$8.9 \pm 3.9^a$	$5.4 \pm 4.0$	$5.3 \pm 3.2$	$4.7 \pm 2.0$
$\beta$ bsh	$1.7 \pm 1.1$	$1.4 \pm 1.1$	$1.4 \pm 1.6$	$2.3 \pm 2.4$
$\beta$ UA	$0.6 \pm 0.4^a$	$0.18 \pm 0.19$	$0.25 \pm 0.24$	$0.13 \pm 0.20$

**Table 5. Comparison of risk for stone formation between normocalciuric and hypercalciuric patients during all the study periods. Statistical significance: <sup>a</sup> $P < 0.001$  compared with all other study periods. <sup>b</sup> $P < 0.05$  compared with baseline and high-calcium study period. <sup>c</sup> $P < 0.01$  compared with all other study periods.**

	Normocalciuric (n = 12)	Hypercalciuric (n = 9)	P
Baseline			
$\beta$ CaOx	$7.3 \pm 3.5^a$	$11.3 \pm 3.3^c$	0.01
$\beta$ bsh	$1.2 \pm 0.8$	$2.5 \pm 1.1$	0.001
Low calcium			
$\beta$ CaOx	$4.1 \pm 2.8$	$7.1 \pm 2.9$	0.02
$\beta$ bsh	$0.7 \pm 0.5^b$	$2.4 \pm 1.0$	0.001
Medium calcium			
$\beta$ CaOx	$3.9 \pm 2.6$	$7.2 \pm 3.0$	0.01
$\beta$ bsh	$0.8 \pm 0.7$	$2.2 \pm 2.1$	0.05
High calcium			
$\beta$ CaOx	$4.3 \pm 2.2$	$5.1 \pm 1.7$	0.01
$\beta$ bsh	$1.3 \pm 0.8$	$3.6 \pm 3.3$	0.05

cantly higher during the high-calcium study period. The alkali content of the high-calcium water caused a reduction in net acid excretion, and this accounted for the significant increase in citraturia.

Table 4 reports the changes in physicochemical conditions of urine during each phase of the study. The addition of any mineral drinking water produced significant decreases in  $\beta$ CaOx and  $\beta$ UA, whereas  $\beta$ bsh varied only marginally. These decreases were similar during the three controlled study periods and were independent of the amount of calcium supplied with the drinking water.

Table 5 shows changes in the most significant risk factors induced by the three types of drinking water in patients grouped as normocalciuric or hypercalciuric. Higher calcium excretions in hypercalciuric patients produced higher  $\beta$ CaOx and  $\beta$ bsh during all the study periods considered. Both groups had a significant decrease in  $\beta$ CaOx upon entering the controlled phases of the study, regardless of the type of water supplied. Increasing the calcium content of the drinking water was not associated with an increase in  $\beta$ CaOx, whereas only marginal increases in  $\beta$ bsh occurred.

Table 6 shows the values of the measured markers of calcium metabolism over the three controlled study periods. Intact PTH and calcitriol levels tended to increase as calcium intake was decreased. Similarly, the two markers of bone resorption increased significantly when patients

changed from the high-calcium to the low-calcium drinking water.

## DISCUSSION

The first objective of the present study was to ascertain whether the use of drinking water of different mineral compositions could result in significant changes to the risk of forming stones in the urine environment. The second was to find out whether bone turnover on a low-calcium diet could be influenced by the mineral content of drinking water. Essentially, we aimed to set a dietary regimen capable of maximally reducing the risk of calcium stone formation without inducing side-effects on calcium and bone metabolism. Taken as a whole, the results obtained fulfil this aim.

It seems pointless to confirm that increasing fluid intake decreases the stone-forming potential in urine. However, those patients who already had relatively low levels of urine saturation in the baseline examinations, further decreased their stone-forming risk when encouraged to drink mineral water. Little is known so far of the relationship between the chemical composition of drinking water and the consequent changes in urine chemistry. Mineral water with a high calcium content was reported to produce urine saturation levels that were equal to or even lower than those found with low-calcium water [18]. Rats fed a low-calcium, oxalate-rich diet had lower calcium oxalate crystaluria when given high-calcium rather than low-calcium water [19]. Hypercalciuric adults given about 600 mg calcium supplements as milk or calcium-fortified orange juice did not increase the risk of calcium oxalate stone formation [20]. It would appear, from these data, that increasing calcium intake through either high-calcium water or other sorts of beverages does not adversely affect urine environment.

In our patients the dilution effect produced by the 700–800 ml increase in urine output, induced by any drinking water, accounted for an overall reduction in calcium oxalate saturation levels compared with the baseline values, which was independent of their calcium content. This effect, however, was caused by changes in urine chemistry that were different for each mineral water. Since diets did not differ during the three controlled phases of the study, it seems reasonable to suppose that the changes observed during the different phases were mostly due to the different chemical compositions of the different types of drinking water. Briefly, equal decreases in calcium oxalate saturation occurred even though the levels of excretion of calcium and oxalate were different. Two factors explain this finding: first, only a fraction of the supplementary calcium supplied with drinking water appeared in the urine; second, these modest increases in calcium excretion were associated with corresponding decreases in oxalate excretion. Concerning the first point, in this study

**Table 6. Variations of calcitropic hormones and proteins and markers of bone resorption during each study period.**  
 Statistical significance: <sup>a</sup>P < 0.05 compared with all other study periods. <sup>b</sup>P < 0.01 compared with low-calcium and P < 0.05 compared with medium-calcium. <sup>c</sup>P < 0.05 compared with low-calcium study period.

Study periods	Low-calcium	Medium-calcium	High-calcium
Intact PTH (pg/ml)	39.8 ± 13.3 <sup>a</sup>	34.6 ± 10.6	32.4 ± 12.8
1,25-dihydroxyvitamin D (pg/ml)	38.2 ± 9.4	35.9 ± 10.2	31.3 ± 8.5 <sup>b</sup>
Osteocalcin (ng/ml)	14.0 ± 3.5	14.0 ± 3.3	13.0 ± 3.0
Hydroxyproline (mg/g creatinine)	24 ± 11	23 ± 13	21 ± 8 <sup>c</sup>
N-telopeptide (nmol/mmol creatinine)	54 ± 28	47 ± 28	32 ± 21 <sup>b</sup>

calcium excretion increased on average by 14.8 to 29.6% of the increments in calcium intake, the lowest values occurring with the highest calcium intake. These results are consistent with others in which changes in calcium intake from different sources caused urinary calcium to change by only 6%, when given as calcium carbonate [21], or 25–35% when given as milk or calcium-fortified orange juice [22].

Intestinal absorption of dietary calcium closely correlates with plasma levels of 1,25-dihydroxyvitamin D [23]. Low calcium intake increases plasma levels of calcitriol [24], and inverse relationships between calcium intake and calcitriol exist [25]. In this study, calcitriol levels decreased when the supplementary calcium of drinking water was added to a low-calcium diet, and this decrease may have played some part in the reduction of the fractional absorption and urinary excretion of calcium at higher calcium intakes. An additional factor which may have contributed to blunting the calciuric response of high-calcium water was a decrease in bone resorption, confirmed by the decrease in urine levels of corresponding markers during the high-calcium study period. This could be accounted for by three factors: first, a decrease in intact PTH induced by the high calcium intake; second, the aforementioned changes in serum calcitriol, which may *per se* modify patterns of bone resorption [26]; third, the alkali supplied with the high-calcium water, which is capable of reducing bone turnover [27].

Concerning the issue of the varying profiles of oxalate excretion during the three phases of the study, it emerges that the different calcium intakes influenced the intestinal absorption of oxalate. Since dietary intakes of both calcium and oxalate were similar during the three controlled study periods, the supplementary calcium given with the drinking water was presumably responsible for the decrease in oxalate intestinal absorption and urinary excretion. Intestinal absorption of oxalate is known to be modulated by calcium concentration in the small intestine [28, 29]. Low-calcium diet was reported to increase the occurrence of mild hyperoxaluria among idiopathic stone-formers [30, 31]. It is also possible that the increases in calcitriol plasma levels observed at the lowest calcium intake could have concurred with the increase in fractional absorption and urinary excretion of oxalate. In fact, 1,25-

dihydroxyvitamin D was shown to increase urinary excretion of orally administered <sup>14</sup>C-oxalate in normal subjects [32] and has been involved in the pathogenesis of hyperoxaluria in calcium nephrolithiasis [33].

Hypercalciuric patients exhibited higher urine saturation with both calcium salts, but this held for all the study periods. In both groups, oxalate excretion tended to decrease at higher calcium intake. In neither group was calcium content of the drinking water crucial to determine the changes in  $\beta$ CaOx.

High-calcium drinking water increased citrate and magnesium excretion. These changes make a significant contribution to decreasing the propensity for calcium stone formation through two distinct mechanisms: first, complexation of calcium and oxalate respectively, which is included in the calculation of  $\beta$  values [16]; second, a direct inhibition of crystal growth and agglomeration, not sought in this study but widely reported in previous studies [34–36]. The inhibition of surface-controlled mechanisms of crystal formation also involves calcium phosphates and counteracts the modest increase in  $\beta$ bsh induced by higher urine pH in patients drinking high-calcium water [34].

This study sums up a number of points which previously had not been thoroughly investigated. The study was performed in a rigorously controlled setting and with a cross-over design. Altogether, these results represent a valuable option for the conservative treatment of a subset of idiopathic calcium stone-formers and apply to both normocalciuric and hypercalciuric patients. The following points are worth emphasizing. First, overall calcium intake may be tailored by supplying drinking water of different calcium contents in order to meet the recommended daily calcium needs. In patients at risk of calcium stone disease, calcium needs may be more safely satisfied by this source than by dairy products, because the latter supply also contains animal protein and salt. These nutrients increase the risk for stone formation through independent changes in urinary calcium, citrate and pH [37, 38] and may promote bone resorption by increasing net acid production and excretion [27]. Second, adverse effects on bone turnover in patients on a low-calcium diet can be prevented by supplying calcium and alkali through drinking water, as suggested by the observed favourable changes in markers of bone resorption with this regimen. Third, these advan-

tages are associated with a reduction in the risk of stone formation at least as effective as that observed when no supplementary calcium is given with drinking water. Fourth, patients who are known to comply with general dietary advice intending to restrict calcium and oxalate and to increase fluid intake, may be easily managed by adapting the composition and amount of drinking water supplied.

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