Efficasy of a citrate-enriched mineral beverage in the prevention of calcium urolithiasis

Učinkovitost s citrati obogatenega mineralnega napitka pri preprečevanju nastanka kalcijevih kamnov v sečilih

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Izvleček

Izhodišča: Namen prispevka je bil ugotoviti, ali je naravni mineralni napitek, obogaten s citrati, učinkovit pri preprečevanju nastanka kalcijevih kamnov v sečilih.

Metode: V prospektivni, randomizirani, enojno slepi raziskavi, ki je trajala dve leti, je sodelovalo 34 bolnikov, 16 moških in 18 žensk, starih od 23 do 71 let (povprečno 50,9 let). Bolniki so bili z žrebom razdeljeni v preiskovano (16) in kontrolno (18) skupino. V raziskavo smo vključili bolnike s ponavljajočimi se kalcijevimi kamni v sečilih, z najmanj 1 recidivom kamnov v zadnjih 2 letih. Pred začetkom raziskave smo pri vseh bolnikih ugotavljali njihove prehranjevalne in pivske navade, njihove demografske in vitalne podatke, kontrolirali smo jim hemogram, biokemične parametre krvi in analizirali njihov 24-urni urin. S pregledno sliko sečil in/ali UZ sečil smo pri vseh bolnikih ugotavljali morebitno navzočnost kamnov v sečilih. Nato so vsi bolniki 2 leti pili napitek 500 ml dnevno. Preiskovana skupina je pila mineralni napitek, obogaten s citrati, kontrolna skupina pa navadno vodo. Ob koncu pitja smo pri vseh bolnikih preverili njihovo zdravstveno stanje in preverili enake laboratorijske podatke kot ob začetku raziskave. Za statistično analizo podatkov smo uporabili pri kvalitativnih spremenljivkah test hi-kvadrat, Fischerjev test in test Cochram-Mante-Haenszel, pri kvantitativnih spremenljivkah pa dvostranski t-test (primerjava skupin) in parni t-test (primerjava podatkov znotraj posamezne skupine).

Rezultati: 24 mesecev po začetku pitja napitkov med skupinama ni bilo statistično značilnih razlik v vrednostih hemograma, biokemičnih parametrov krvi in v vrednostih parametrov 24-urnega urina. Znotraj preiskovane skupine pa je prišlo do statistično značilnega porasta koncentracije magnezija ($p = 0.0047$), fosfatov ($p = 0.0103$) in citratov ($p = 0.0410$). V kontrolni skupini se je v 24-urnem urinu statistično pomembno zmanjšala specifična teža urina ($p = 0.0137$), povečala pa se je vrednost kalcija ($p = 0.0382$) in magnezija ($p = 0.0068$). V preiskovani skupini se je prav tako statistično pomembno zmanjšal litogeni indeks kalcij/magnezij ($p = 0.0049$). Med preiskovano in kontrolno skupino ni bilo statistično pomembnih razlik glede števila kamnov v sečilih, tako pred pitjem ($p = 0.7125$) kot po pitju napitka ($p = 0.2297$). 88 % bolnikov v preiskovani skupini in 83 % v kontrolni skupini je bilo z napitkom zadovoljnih ali zelo zadovoljnih. Zaradi slabega prenašanja napitka so predčasno zaključili z raziskavo 2 bolnikov v preiskovani skupini in 1 bolnika v kontrolni skupini.

Zaključki: Na osnovi naše raziskave lahko sklepamo, da bi bil lahko mineralni napitek, obogaten s citrati, učinkovit zaviralec kristalizacije kalcijevih kamnov v sečilih. Temu v prid govori predvsem statistično pomembno povišanje inhibitorjev urolitiaze.

Abstract

Background: The aim of our study was to evaluate the efficacy of a new citrate-enriched natural mineral beverage in the prevention of calcium stone formation in the urinary tract.

Methods: Thirty-four patients, 16 male and 18 female, between 23 and 71 years of age (average 50.9 years), participated in a prospective, randomized, single-blind study that lasted two years. The patients were randomly divided into a study group (16 patients) and a control group (18 patients). All patients suffered from recurrent urinary calcium stone disease, with at least one recurrence experienced within the previous two years. Before the start of the study, we evaluated the patients' dietary habits and fluid intake, recorded the demographic and vital data, performed a blood count, biochemical analysis of blood and analysis of a 24-hour urine specimen, and obtained a plain x-ray film and/or ultrasound scan of the urinary tract to establish the presence of any urinary stones. Over the following two years, the patients of the study group drank 500 ml of the citrate-enriched mineral beverage daily, while the patients of the control group drank the same quantity of plain water. At the end of this treatment, each patient's health status was assessed and the initial laboratory investigations were repeated. Statistical analysis of the results was performed with the use of the chi-square test, Fischer's test and the Cochram-Mante-Haenszel test for qualitative variables; the two-tailed t test (comparison between groups) and the paired t test (comparisons within individual group) were used for quantitative variables.

Results: At the end of the 24-month treatment period, there were no significant differences between the groups in any values of the blood cell count, biochemical parameters of blood or parameters of 24-hour urine. Results for the study group showed a significant increase in urinary magnesium ($p = 0.0047$), phosphate ($p = 0.0103$) and citrate ($p = 0.0410$) over the baseline values. In the control group, values for 24-hour urine showed a significant decrease in specific gravity ($p = 0.0137$) and a significant increase in the levels of calcium ($p = 0.0382$) and magnesium ($p = 0.0068$). In the study group, the calcium/magnesium ratio in urine was significantly below the baseline value ($p = 0.0049$). The number of stones in the urinary tract did not differ significantly between the two groups either before ($p = 0.7125$) or after the treatment ($p = 0.2297$). Eighty-eight per cent of patients in the study group and 83% of those in the control group were satisfied or highly satisfied with the treatment received. Two patients in the study group and one in the control group were excluded from the study because of gastrointestinal intolerance.

Conclusions: On the basis of our study, we can conclude that the citrate-enriched mineral beverage might prove an effective inhibitor of calcium stone formation in the urinary tract. This is supported mainly by the observed significant increase in urolithiasis inhibitors.

Introduction

Between 70 and 80 per cent of urinary stones are composed of calcium salts, mostly calcium oxalate and calcium phosphate.[1] The majority of these stones recur within 5 years of initial appearance. Calicum stones represent a major problem because of the variable clinical course and aetiology, and numerous secondary diseases.[2]

The principal causes of idiopathic calcium urolithiasis are environmental influences, metabolic disorders and genetic factors.[3] Nutrition is considered to be one of the most important environmental factors.[4] The main metabolic disorders in recurrent calcium stone disease are hypercalciuria (39 %), hyperoxaluria (32 %), hypocitraturia (29 %), hyperuricuria (23 %) and hypomagnesiuria (19 %).[5]

A single biochemical variable that could predict the course of the disease has not been identified so far. It is known, however, that patients who have formed more than one urinary stone are more likely to have a recurrence than patients who have formed a single stone.[6] It has also been demonstrated that males have a 2–4 times higher prevalence of calcium stones than females, and that a higher phosphate content of stones may signify a greater risk of recurrence.[7]

The prophylaxis of recurrent calcium stones in the urinary tract is difficult and often controversial. Many authors feel that it is better to remove the stones than to spend time and money to prevent their formation. However, recent data suggest that preventive treatment is economically justified.[2]

Theoretically, a sufficient fluid intake seems to be a logical preventive measure, which has been also confirmed by studies.[8] It has also been demonstrated that a high intake of meat protein increases the excretion of calcium and oxalate in urine.[9] Inadequate dietary intake of calcium leads to increased intestinal absorption of oxalate and hyperoxaluria.[10] Therefore patients with recurrent urinary calcium stones are advised to avoid excessive intake of meat protein and salt, but to maintain a normal dietary intake of calcium.[11]

Three types of drugs – thiazides, alkaline citrates and allopurinol – have been shown to be effective in the prevention in urinary stones.[2] However, a meta-analysis of 14 articles demonstrated significant efficacy only for thiazides.[12] Potassium citrate and potassium-magnesium citrate have also been found to be effective, but either the number of patients treated was too small or the duration of treatment was too short for the data obtained to be valid for statistical analysis.

Mineral waters have been used in the prevention of urinary stone formation for a long time. The intake of mineral water enhances the diuresis, alters the pH of urine, and increases the concentration of magnesium and citrate ions, which cause lithogenic substances to become more soluble in urine. Mineral waters are also known to have an anti-inflammatory effect.[13]

In one study, the use of a natural mineral water with a high content of magnesium and hydrogen carbonate ions, significantly increased urinary excretion of magnesium and citrate and caused the pH of urine to shift into the neutral range.[14]

In another study, the administration of a natural mineral water enriched with citrate and vitamins to patients with recurrent urinary calcium stones over a period of 14 days led to a significant increase in urinary citrate, magnesium and pH, accompanied by a reduction in urinary calcium.[15]

The aim of our study was to evaluate the efficacy of a citrate-enriched natural mineral beverage in preventing the formation of new calcium stones in the urinary tract.

Table 1: Analysis of the citrate-enriched natural mineral beverage

Composition	Concentration (mmol/L)
Citrate ($C_6H_5O_7^{3-}$)	4.76
Potassium (K^+)	15.38
Magnesium (Mg^{2+})	41.15
Sodium (Na^+)	69.59
Calcium (Ca^{2+})	9.98
Sulphate (SO_4^{2-})	22.92
Hydrogencarbonate (HCO_3^-)	131.15
Total	**294.93**

Table 1: Analysis of plain water

Composition	Concentration (mmol/L)
Magnesium (Mg^{2+})	3.42
Sodium (Na^+)	3.02
Calcium (Ca^{2+})	1.99
Sulphate (SO_4^{2-})	1.15
Hydrogencarbonate (HCO_3^-)	11.59
Total	**21.17**

Methods

The study was approved by the Medical Ethics Committee of the Republic of Slovenia. It was conducted in the form of a prospective, randomized, single-blind trial lasting two years, and included 34 patients (16 males and 18 females) between 23 and 71

Table 2: Analysis of 24-hour urine before and after treatment, by groups

		Study group		Control group		p-value (difference between groups)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Volume	N	14	14	14	14		
	mean	2.111	2.393	1.796	1.986	0.1823	0.1244
	SD	0.624	0.716	0.592	0.638		
	min,max	1.4, 3.8	1, 3.9	0.9, 2.8	0.8, 2.9		
Specific	N	12	12	12	12		
gravity	mean	1018.2	1018.8	1022.5	1017.9	0.1091	0.7063
	SD	7.2	5.3	5.4	5.4		
	min,max	1005,1030	1015,1030	1015,1030	1010,1030		
Osmolarity	N	10	10	9	10		
	mean	1156.7	1123.1	1123.6	881.7	0.8798	0.1558
	SD	414.3	378.3	525.2	349.9		
	min,max	578, 1984	610, 1719	673, 2113	494, 1531		
pH	N	14	14	15	15		
	mean	6.236	6.333	6.241	6.421	0.9823	0.6814
	SD	0.660	0.652	0.527	0.480		
	min,max	5.07, 7.4	5.11, 7.69	5.34, 6.9	5.46, 7.3		
Ca++	N	13	13	15	14		
	mean	7.739	7.348	7.459	9.291	0.8253	0.1141
	SD	3.049	3.133	3.535	3.035		
	min,max	3.9, 14.3	1.62,11.65	1.3, 15.3	4, 13.56		
Mg++	N	13	13	15	13		
	mean	3.464	6.461	5.065	7.425	0.0541	0.3536
	SD	2.075	2.215	2.111	2.935		
	min,max	0.8, 7.4	3.1, 10.26	2.13, 9.26	3.51,15.06		
Urate	N	13	13	15	15		
	mean	3.119	4.290	4.253	4.083	0.0714	0.7571
	SD	1.689	1.984	1.507	1.510		
	min,max	0.6, 6	0.9, 7.8	2.3, 7.6	2.3, 6.95		
Oxalate	N	14	14	13	14		
	mean	232.1	281.6	278.0	349.9	0.3517	0.2658
	SD	125.6	135.6	125.8	179.1		
	min,max	72.9, 431	82, 577	123, 649	122, 652		
Phosphate	N	13	13	15	15		

		Study group		Control group		p-value (difference between groups)	
	mean	20.52	31.35	24.33	26.98	0.4120	0.4055
	SD	11.29	15.09	12.69	12.23		
	min,max	4.9, 43.5	11.1, 60.6	10.2, 51.1	10.8, 49.3		
Citrate	N	14	14	14	14		
	mean	2.993	4.16	3.964	5.061	0.1269	0.1384
	SD	1.761	1.271	1.488	1.825		
	min,max	0.32, 5.7	1.7, 6.2	1.6, 5.96	1.92, 8.42		
Creatinine	N	14	14	15	15		
	mean	11.344	13.893	12.907	12.113	0.4809	0.4250
	SD	7.224	7.435	4.273	3.447		
	min,max	1.98, 25.8	4.1, 31.5	7.5, 21.6	6.9, 19.8		
Titra.	N	11	11	14	14		
	mean	26.378	30.745	30.661	28.329	0.5346	0.7148
	SD	12.511	15.277	19.555	16.895		
	min,max	2.90, 43.3	8.1, 66.7	6.75, 72.8	4.5, 66.4		
Amon	N	13	13	15	15		
	mean	40.854	47.858	48.351	53.16	0.3483	0.5857
	SD	21.767	23.760	19.766	26.638		
	min,max	14.34, 88	16.3,103.2	21.7, 93.3	26, 118.9		

years of age (average 50.9 years). All subjects had proven recurrent urinary calcium stones with at least one recurrence within the previous two years and no renal colic or intervention for calculous disease within the previous three months.

Excluded from the study were patients with obstructive uropathy, chronic urosepsis, renal failure (serum creatinine > 150 mm/L), renal tubular acidosis, sarcoidosis, hyperparathyroidism or inflammatory bowel disease. Also excluded were patients taking steroids, diuretics, various vitamins and minerals, and patients with proven primary hyperoxaluria, staghorn calculi, cystine or urate calculi or a sponge kidney. None of the patients had hyperuricosuria, diabetes or hyperkalaemia, and none was taking any drugs for the control of stone disease. Additional exclusion criteria for women were pregnancy and lactation.

Before the start of the study, all subjects underwent a baseline evaluation, which comprised the patient's dietary habits (type of foods and fluids ingested), use of alcohol and tobacco, demographic data (age, gender), body mass and height, blood pressure, heart rate, presence of other diseases (urinary tract infection), and possible presence of calculous disease in the family. Each patient had a basic clinical examination and laboratory investigations, including a blood count, biochemical analysis of blood, and analysis of a native urine specimen and a 24-hour urine specimen (volume, specific gravity, osmolarity, pH, calcium, magnesium, urate, oxalate, phosphate, citrate and creatinine). A plain abdominal x-ray film and/or an ultrasound scan were obtained to detect any calcium stones present in the urinary tract.

The patients were advised of the study design and gave their informed consent for the study. They were randomly divided into a study group (16 subjects) and a control group (18 patients). The study group drank citrate-enriched mineral water, and the con-

trol group drank plain water (Table 1). Both beverages were supplied in 500 ml bottles of identical appearance with identical labels. Both groups drank the beverages according to the following schedule: 100 ml after breakfast, 100 ml after lunch, 150 ml after dinner and 150 ml before sleep.

The patients were instructed to continue drinking all other fluids in the same quantities and to follow the same diet as before the study.

All patients were re-evaluated after drinking the study beverages for 6, 12, 18 and 24 months. At each follow-up visit, a history was obtained, the initial examinations (physical examination, blood count, biochemical analysis of blood and 24-hour urine, ultrasound and/or x-ray examination of the urinary tract) were repeated, and possible side-effects of the beverages were recorded. At the final visit, we also calculated the urinary calcium/urinary magnesium ratio and the urinary oxalate/urinary citrate ratio for each patient. At the end of the study, the researchers made a subjective appraisal of the effect of the prophylactic regimen in each patient and asked the patient for his/her opinion about the treatment received.

Statistical methods: Comparison of the groups for the qualitative variables was performed with the chi-square test, Fischer's exact test and the Cochram-Mante-Haenszel test. The quantitative variables of both groups were compared with the two-tailed t-test for independent samples, and changes within individual groups with the paired t-test. In case of a non-normal data distribution, appropriate non-parametric tests (Wilcoxon's tests) were employed.

Results

Before the start of treatment, the study group (16 patients) and the control group (18 patients) were compared with regard to dietary habits, demographic and vital characteristics (age, height, weight, blood pressure, heart rate), prevalence of urinary tract infection, family history of urinary stone disease and clinical examination. No statistically significant differences were found between the groups.

At the end of the study, after 24 months of treatment, there were no statistically significant differences between the groups regarding body weight, blood pressure and heart rate. Also the number of renal colics (experienced during the treatment) was comparable between the groups: 4 in the study group and 6 in the control group. With the exception of one patient in the study group, the subjects had had no intercurrent diseases. Most patients showed good tolerance for the beverages; only two patients (12.5 %) in the study

Table 3: Indicators of lithogenic risk in urine (Ca/Mg, oxalate/citrate)

		Study group		Cntrol group		p-value (difference between groups)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatm.	After treatm.
Ca/Mg	N	12	12	15	12		
	mean	3.49	1.13	1.77	1.38	0.0947	0.3040
	SD	3.12	0.49	1.24	0.65		
	min,max	0.81,11.5	0.39,2.08	0.29, 4.8	0.56,2.59		
Oxalate/	N	14	14	13	14		
citrate	mean	125.14	73.4	76.3	71.2	0.1444	0.8725
	SD	112.5	39.4	37.7	31.7		
	min,max	19.5,359.4	19.5,151.8	35.3,176.3	22.9,151.8		

group and one (5.6 %) in the control group had gastrointestinal symptoms (diarrhoea) due to the treatment.

The blood count parameters showed no significant differences between the groups either before or after the treatment (two-tailed t-test, non-parametric Wilcoxon's test).

The biochemical parameters of blood, with the exception of the pre-treatment alkaline phosphatase level, which was higher in the study group ($p = 0.0041$), also did not differ between the groups either before or after the treatment (two-tailed t-test, non-parametric Wilcoxon's test).

The parameters of 24-hour urine showed no significant differences between the two groups either before or after the treatment (Table 2).

Analysis of the changes in individual parameters of 24-hour urine within each group showed a significant increase in the levels of magnesium ($p = 0.0137$), phosphate ($p = 0.0103$) and citrate ($p = 0.0410$) in the study group.

In the control group, the specific gravity of 24-hour urine decreased significantly ($p = 0.0137$), while the levels of calcium and magnesium showed a significant increase ($p = 0.0382$, $p = 0.0068$).

The concentration of magnesium in urine increased in 84.6 % of patients in the study group and in 76.9 % in the control group. Citrate increased in 85.7 % of patients in the study group and in 64.3 % of patients in the control group.

At the end of the study, the calcium/magnesium and oxalate/citrate ratios in urine revealed no significant differences between the groups (Table 3).

Analysis of the changes in these ratios within individual groups showed a significant decline in the calicum/magnesium ratio in the study group ($p = 0.0049$) (Table 4).

In the study group, the calcium/magnesium ratio decreased in 87.5 % of patients, while the oxalate/citrate ratio decreased in 59.3 % of patients.

Fourteen patients in the study group had a total of 19 kidney stones sized 2–6 mm before the treatment, and 13 patients in this group had a total of 17 stones sized 3–10 mm after the treatment. Therefore, no significant changes in the number of urinary stones occurred during the study. Over the 2-year study period, the status regarding the number of stones deteriorated in one subject and improved in four subjects.

In the control group, 13 patients had a total of 20 stones sized 3–10 mm before the treatment, and nine had 16 stones seized 2-10 mm after the treatment. Therefore, no significant changes in the number of stones occurred during the study ($p = 0.3173$). The status regarding the number of stones present in the urinary tract improved in seven patients; an increase in the number of stones after the treatment was observed only in two patients.

The number of stones did not differ significantly between the groups either be-

Table 4: Indicators of lithogenic risk in urine: changes within each group

		Study group	Control group	p-value (difference between groups)
Ca/Mg	N	12	12	
	mean	-2.36	-0.31	0.0565
	SD	3.25	0.92	
	p-value	0.0049*	0.2599	
Oxalate/citrate	N	14	13	
	mean	-51.76	-5.58	0.1659
	SD	109.21	47.07	
	p-value	0.0996	0.6766	

fore (p = 0.7125) or after the treatment (p = 0.2297).

Subjective appraisal of the results of the prophylactic treatment and the gastrointestinal tolerance on the part of the patients and the research team is presented in Table 5. The researchers' ratings are similar for both groups. The patients' ratings show, however, that the study group was somewhat more satisfied with the treatment than the control group, but the differences are statistically insignificant (p = 0.1803). Fourteen patients (87.5 %) from the study group and 17 patients (94.4 %) from the control group completed the treatment according to the protocol. Three patients (2 from the study group and 1 from the control group) left the study because of gastrointestinal intolerance.

Discussion

The aim of prophylactic measures in patients with recurrent urinary stones is normalization of the biochemical composition of their urine. The biochemical changes of urine observed in our study show that the citrate-enriched mineral beverage could efficiently prevent new stone formation in the urinary tract.

Our study lasted only 2 years. However, some authors believe that studies of the efficacy of specific measures for the prevention of urinary calculi should last at least 5–6 years, and most such studies last about 3 years. The average reccurrence rate of urinary calculi is 0.15 to 0.20 stones per year.[2]

We studied prospectively 34 patients with recurrent calcium urolithiasis. Sixteen patients were assigned into the study group, to be treated with citrate-enriched mineral water; 18 patients formed the control group, which received plain water. A total of 64 patients participated in a similar study by Ettinger and co-workers,[16] and 38 patients completed a study on the influence of potassium citrate on calcium stone formation, performed by Barcelo and co-workers.[17] The comparatively small number of patients in our study could affect mainly our clinical results about the prevalence of stones prior to and following treatment.

Before the start of our study, we observed no differences between the two groups: most of our patients were non-smokers, most abstained from alcohol, had a varied diet and drank different beverages. We included in our study patients of both genders, although the composition of urine differs between the sexes and is known to be more age-dependent in women.[13]

The patients in both groups were aged 50 years on average, which is 3–6 years more than in other studies.[16,17] They had a normal blood pressure and pulse rate and were free from urinary tract infection. A half of our patients had a positive family history of urinary stones.

Table 5: Gastrointestinal tolerance and subjective appraisal of the prophylactic regimens by patients and the research team

		Study group	Control group	p-value (difference be-tween groups)
Researchers' ratings	effective	11 (68.75%)	12 (66.67%)	0.9771
of prophylactic	partly effective	3 (18.75%)	4 (22.22%)	
regimens	ineffective	2 (11.5%)	2 (11.11%)	
Patients' satisfaction	highly satisfied	11 (68.75%)	7 (38.89%)	0.1803
	satisfied	3 (18.75%)	8 (44.4%)	
	dissatisfied	2 (11.5%)	3 (16.67%)	
Gastrointestinal	good	14 (87.5%)	17 (94.44%)	0.5909
tolerance	poor	2 (12.5%)	1 (5.56%)	

Before treatment, the two groups did not differ in blood count values and biochemical parameters of blood. All patients had their electrolyte, creatinine and urea values within the normal range.

Analysis of 24-hour urine before the start of treatment revealed no statistically significant differences between the study group and the control group. The levels of magnesium, citrate and oxalate were within the normal range. Several previous studies have recommended limiting the preventive use of citrates to patients with hypocitraturia.[18] In the study of Ettinger and co-workers,[16] less than 20 % of patients had reduced citrate levels in their 24-hour urine, and the authors therefore recommended non-selective use of citrate for the prevention of calcium stones. Also in our study, patients with recurrent calcium stones were enrolled, regardless of their urinary citrate levels.

The patients in our study group drank the mineral beverage for 2 years. The beverages used in the study group and the control group differed mainly in the levels of citrate, magnesium and bicarbonate. The daily intake of the beverages was 500 ml, distributed over the entire day, with 150 ml ingested at bedtime. Perhaps the quantity of the beverages and the distribution of their intake over the day should have been different and a greater quantity should have been ingested before sleep, when the likelihood of crystal formation in urine is highest.

After two years of this treatment, our patients showed no significant changes in their vital and demographic parameters. The body weight, blood pressure and heart rate remained unchanged in both groups. Also the blood count and biochemical blood parameters revealed no significant changes in either group, except the pretreatment alkaline phosphate level which was higher in the study group.

Both beverages had a significant effect on the volume of excreted urine and its biochemical composition. In both groups, the volume of urine increased insigificantly, whilst its osmolarity declined despite the increased intake of electrolytes. So the reduced rate of new stone formation observed in our study could be attributed solely to the the effect of the beverages. Many authors claim that fluid intake alone is the most powerful and the most economical measure for preventing new stone formation in the urinary tract and that patients with recurrent calcium stones excrete a smaller quantity of urine than healthy people.[19]

It is known that the solubility of most lithogenic substances in urine is strongly dependent on the pH of urine.[14] Stones composed of uric acid, cystine and calcium oxalate are less soluble when the pH of urine is below 6. Stones made of calcium phosphate, calcium carbonate, calcium carbonate-phosphate and magnesium ammonium-phosphate are less soluble in urine with a pH below 7. Lithogenic substances dissolve most readily when the pH of urine is between 6 and 7.[20]

In our study, urinary pH in both groups of patients showed an insignificant increase – by 0.09 in the study group and by 0.18 in the control group. Other researchers have obtained similar results. Prevorčnik and co-workers (14) report an increase in the average pH value of urine from 6.04 to 6.36 after daily ingestion of 400 ml of mineral water for 14 days. In two other studies, the use of potassium-magnesium citrate led to an insignificant increase in urinary pH from 6.01 to 6.29,[16] while the use of potassium citrate caused the average urinary pH to increase from 5.4 to 6.0.[17]

At the end of our study, the urinary magnesium levels in both groups of patients were significantly above the pre-treatment values. The average urinary excretion of magnesium increased significantly from 3.464 mmol/L to 6.461 mmol/L in the study group ($p = 0.0137$) and insignificantly from 5.065 mmol/L to 7.425 mmol/L in the control group. The difference between the groups was insignificant.

In two other studies, a significant increase in urinary magnesium was observed after the use of potassium magnesium citrate[16] and after drinking a natural mineral water.[14]

Magnesium is a known inhibitor of calcium stone formation in urine. Twenty percent of the inhibitory potential of urine is ascribed to it.[21] However, its role in patients with idiopathic calcium nephrolithiasis has not been fully clarified. In one study,[24] the

recurrence rate of renal stones was observed to decrease after the use of magnesium oxide and magnesium hydroxide; the treatment led to the formation of magnesium oxalate, which was more soluble than calcium oxalate.[20] Magnesium is also believed to reduce oxaluria by inhibiting the biosynthesis of oxalate in the liver.[25]

In patients with recurrent calcium urolithiasis, the calcium/magnesium ratio in urine is a more reliable indicator of the risk of stone formation than the absolute magnesium level.[26] In our study, the calcium/magnesium ratio, also known as the lithogenic risk index, decreased significantly ($p = 0.0049$) in 87.5 % of patients in the study group. This result indicates that the citrate-enriched mineral beverage was a more effective inhibitor of crystal formation in urine than plain water.

Citrate in urine is thought to be the principal inhibitor of calcium urolithiasis. Nearly 50 % of the inhibitory activity of urine is ascribed to citrate.[27] Citrate binds calcium ions into soluble complexes, thus reducing the saturation of urine with calcium ions and preventing the formation of calcium oxalate and calcium phosphate crystals.[28] Hypocitraturia is the most frequent metabolic disorder in patients with calcium urolithiasis.[29]

In our study, 85.7% of patients in the study group had significantly elevated urinary citrate levels ($p = 0.0103$) after drinking citrate-enriched mineral water for 2 years, whereas only 64.3 % of patients in the control group showed a moderate, statistically insignificant increase in urinary citrate after drinking plain water for the same period of time. Neither of the groups in our study showed a significant change in urinary excretion of oxalate.

Our findings agree with those of Prevorčnik and co-workers,[14] who observed a significant increase in urinary excretion of citrate but no change in urinary excretion of oxalate after the subjects drank a natural mineral beverage for 14 days.

In our study, the oxalate/citrate ratio decreased insignificantly in the study group ($p = 0.09$). In the control group, the decrease in this ratio was only minimal. Other researchers also reported a significant decrease in the oxalate/citratre ratio after the intake of natural mineral water.[14]

In a study lasting 3 years, Barcelo and co-workers[17] demonstrated a significant increase in the urinary level of citrate in 18 patients with idiopathic calcium nephrolithiasis already after 3 months of treatment with potassium citrate. The pH of urine was between 6.0 and 6.5. The authors concluded that citrate and alkalization of the urine were the main factors responsible for the reduced rate of new stone formation observed in their subjects. Similar results were reported by other authors.[14] A significant increase in urinary citrate was observed also in a group of patients with recurrent calcium oxalate urinary stones who were treated with potassium magnesium citrate, but the increase in urinary pH in that group was only marginal.[16] So the reduction in new stone formation achieved in these studies could be explained with the alkalization of urine and elevated urinary levels of citrate and magnesium. Experimental studies have shown that magnesium citrate prolongs the time of agglomeration of crystals in urine and that the low oxalate tolerance in patients with idiopathic calcium stones is the consequence of a low urinary level of free citrate and a low urinary pH.[23]

In our study, the 24-hour urine of patients in both groups also showed some other biochemical changes after the treatment. Calcium increased insignificantly in 53 % of patients in the study group and significantly in 64.3 % of patients in the control group. Phosphate increased significantly in 84.6 % of patients in the study group and insignificantly in 53.3 % of patients in the control group.

Chow and co-workers[30] have demonstrated experimentally that citrate inhibits the growth of calcium oxalate crystals in urine. At the end of a 33-day study period, the average weight of stones in urine containing 2 mM of citrate was 169.9 mg, while stones in urine containing 6 mM of citrate had an average weight of 127.2 mg ($p < 0.001$).

In our study, both beverages ingested by the subjects daily for 2 years were effective in preventing the formation and growth of urinary stones. The differences in new stone formation between the groups were insignificant. In the study group, comprising 16 patients, 14 patients had 19 stones at the beginning of treatment, and 13 had 17 stones

at the end of treatment. In the control group, composed of 18 patients, 13 had 20 stones at the beginning of treatment, and 9 had 16 stones at the end of treatment. The study thus showed that both beverages were about equally effective clinically. One of the reasons why the mineral beverage with a higher content of urolithiasis inhibitors did not prove more effective is probably related to the clearly positive effect of the increased intake of fluids, which did not, however, interfere with the activity of the natural inhibitors of crystalization.[8] It is also possible that our clinical results would have been different if the study had lasted longer and if more patients had been enrolled.

The efficacy of potassium-magnesium citrate in the prevention of recurrent calcium urolithiasis has been demonstrated also by other authors. In a study lasting 3 years, Ettinger and co-workers[16] observed new stone formation in 63.6 % of patients receiving placebo and in only 12.9 % of those treated with potassium-magnesium citrate.

Barcelo and co-workers[17] showed potassium citrate to be clinically effective in patients with idiopathic calcium nephrolithiasis and hypocitraturia. After 3 years of taking the medication, as many as 72 % of their patients experienced a remission of the disease, while the remission rate in the control group was only 20 %.

The beverages used in our study caused relatively few side-effects: only two patients (12.5 %) in the study group and one (5.5 %) in the control group complained of gastrointestinal symptoms and left the study before its termination. Similarly, in two other studies, gastrointestinal intolerance was observed in 11.5 % of patients receiving potassium-magnesium citrate[16] and in 9 % patients treated with potassium citrate.[17]

The regimens given to the study group and the control group for the prevention of calcium stone formation were assessed as effective both by the patients and the research team.

Conclusions

Our study has demonstrated that natural citrate-enriched mineral water is effective in preventing new calcium stone formation in the urinary tract. The treatment led to a significant increase in urinary levels of citrate, magnesium and bicarbonate, a significant decline in the calicum/magnesium ratio, and a nearly significant change in the oxalate/citrate ratio. The mineral beverage may be recommended mainly as a nutritional supplement since it contains all principal inhibitors of urinary stone formation: citrate, magnesium and bicarbonate.

Prophylactic treatment in the form of a mineral drink offers the advantage of increasing the intake of fluids, besides providing the patient with magnesium and citrate. Patients should be advised to drink at least 500 ml citrate-enriched mineral beverage before sleep, in addition to smaller quantities ingested over the day.

Our study had several limitations. The number of subjects was relatively small and the duration of the study was too short to allow definitive assessment of the efficacy of this new mineral drink in the prevention of urinary stone formation.

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