

Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial^{1–3}

Antonio Nouvenne, Tiziana Meschi, Beatrice Prati, Angela Guerra, Franca Allegri, Giuseppe Vezzoli, Laura Soldati, Giovanni Gambaro, Umberto Maggiore, and Loris Borghi

ABSTRACT

Background: A direct relation exists between sodium and calcium excretion, but randomized studies evaluating the sustained effect of a low-salt diet on idiopathic hypercalciuria, one of the main risk factors for calcium-oxalate stone formation, are still lacking.

Objective: Our goal was to evaluate the effect of a low-salt diet on urinary calcium excretion in patients affected by idiopathic calcium nephrolithiasis.

Design: Patients affected by idiopathic calcium stone disease and hypercalciuria (>300 mg Ca/d in men and >250 mg Ca/d in women) were randomly assigned to receive either water therapy alone (control diet) or water therapy and a low-salt diet (low-sodium diet) for 3 mo. Twenty-four-hour urine samples were obtained twice from all patients: one sample at baseline on a free diet and one sample after 3 mo of treatment.

Results: A total of 210 patients were randomly assigned to receive a control diet ($n = 102$) or a low-sodium diet ($n = 108$); 13 patients (2 on the control diet, 11 on the low-sodium diet) withdrew from the trial. At the follow-up visit, patients on the low-sodium diet had lower urinary sodium (mean \pm SD: 68 ± 43 mmol/d at 3 mo compared with 228 ± 57 mmol/d at baseline; $P < 0.001$). Concomitant with this change, they showed lower urinary calcium (271 ± 86 mg/d at 3 mo compared with 361 ± 129 mg/d on the control diet, $P < 0.001$) and lower oxalate excretion (28 ± 8 mg/d at 3 mo compared with 32 ± 10 mg/d on the control diet, $P = 0.001$). Urinary calcium was within the normal range in 61.9% of the patients on the low-salt diet and in 34.0% of those on the control diet (difference: +27.9%; 95% CI: +14.4%, +41.3%; $P < 0.001$).

Conclusion: A low-salt diet can reduce calcium excretion in hypercalciuric stone formers. This trial was registered at clinicaltrials.gov as NCT01005082. *Am J Clin Nutr* 2010;91:565–70.

INTRODUCTION

According to one of the most widely accepted criteria, hypercalciuria is defined as the daily urinary excretion of >300 mg Ca/d (7.5 mmol) in men and >250 mg Ca/d (6.25 mmol) in women while on a regular unrestricted diet. Hypercalciuria is believed to be an important risk factor for the crystallization of calcium oxalate and the formation of kidney stones (1). When not caused by pathologic conditions or drugs known to increase urinary calcium excretion, the disorder is qualified as idiopathic. Idiopathic hypercalciuria was shown in 30–50% of calcium-oxalate stone formers (2, 3). Although genetic factors undoubtedly play an important role in its cause (4), the type of diet

(ie, an excessive intake of calcium, sodium chloride, and animal proteins) and a low intake of alkaline potassium salts may influence its phenotypic expression (5, 6).

In industrialized countries the diet is characterized by a strong and widespread excess of sodium chloride taken discretionarily as salt added to home-prepared foods and, in a much greater proportion, nondiscretionarily as salt contained in industry-manufactured foods. The salt that is usually ingested with food exceeds the physiologic requirement by 8–10 times (7).

Regarding dietary salt intake, estimates based on food composition tables and the anamnestic report of the amount added to home-prepared food are unreliable, whereas the methods based on the measurement of urinary sodium and chloride excretion are much more trustworthy (8).

Studies showed a close relation between sodium and calcium excretion in healthy subjects and calcium stone formers, with the sodium chloride dietary load increasing urinary calcium excretion (9, 10) and the sodium chloride dietary withdrawal decreasing urinary calcium excretion in healthy subjects and calcium stone formers (11–17). The decrease in calciuria obtained by a dietary sodium withdrawal of 100 mEq amounted to 80–100 mg, an effect similar to that obtained with the use of thiazide diuretics (12–14, 16). However, these studies were conducted on small populations for very short periods (only a few days) and lacked a control group; therefore, they cannot be considered conclusive.

On the basis of these considerations, we carried out a randomized controlled trial on calcium stone formers for a period of 3 mo with the aim of evaluating the effect of a low-salt diet on idiopathic hypercalciuria.

¹ From the Departments of Clinical Sciences (AN, TM, BP, AG, FA, and LB) and Clinical Medicine, Nephrology, and Prevention Sciences (UM), University of Parma, Parma, Italy; the Nephrology Unit, San Raffaele Hospital, Milan, Italy (GV); the Department of Sciences and Biomedical Technologies, University of Milan, Milan, Italy (LS); and the Division of Nephrology, Columbus-Gemelli Hospital, Catholic University, Rome, Italy (GG).

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³ Address correspondence to A Nouvenne, Department of Clinical Sciences, University of Parma, Via A Gramsci 14, 43100 Parma, Italy. E-mail: antonio.nouvenne@alice.it.

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SUBJECTS AND METHODS

Study population

This trial is a subproject of a wider-reaching multicenter study on the genetic and nutritional determinants of idiopathic calcium-oxalate stone disease in adults aged 18–65 y. The study was approved by the Ethical Committee of the University of Parma.

All patients were enrolled through the specialist out-patient clinic of the University Hospital of Parma (Parma, Italy), which has followed a standardized screening protocol for stone disease since 1984.

Patients had to fulfill the following requirements to be enrolled in this study: 1) a diagnosis of idiopathic calcium-oxalate stone disease made on the basis of at least one stone expelled and analyzed by infrared spectrophotometry; 2) the absence of diseases known to be associated with the production of calcium stones (eg, primary hyperparathyroidism, primary hyperoxaluria, enteric hyperoxaluria, bowel resection, inflammatory bowel disease, renal tubular acidosis, sarcoidosis, sponge kidney, and hyperthyroidism); and 3) no chronic use of drugs capable of increasing the risk of calcium stone formation, such as vitamin D, acetazolamide, and antiepileptic drugs.

Additional requirements for patient enrollment were as follows: perfect mental and physical health, free from diabetes mellitus, no episode of renal colic in the preceding 3 mo, no retained stone, no long trip or holiday away from home planned for the next 3 mo, no intention of chronic use of drugs or supplements for the next 3 mo, systolic blood pressure >110 mm Hg (measured at rest in a sitting position with a manual mercury sphygmomanometer), normal kidney function, and daily urinary excretion of >100 mmol Na and Cl/d and >300 mg Ca/d (7.5 mmol) in men and >250 mg Ca/d (6.25 mmol) in women while on a free diet.

For 3 consecutive years starting on 1 January 2005, men and women who fulfilled the enrollment criteria were invited to participate in the trial. All subjects enrolled in the trial were informed that the treatment would consist of either water therapy alone (control diet) or water therapy plus salt-intake reduction, and after 3 mo (at the follow-up visit) they should perform an additional urine check.

The only incentives offered to the participants were the following: a free supply of water drinks, having leading study physicians at their disposal for any medical need arising during the study duration, and free urine tests, even after completion of the study.

Every subject who fulfilled the selection criteria and signed an informed consent form was randomly assigned to 1 of the 2 treatments. Randomization was stratified according to sex. A computer program was used to generate the 2 sequences of random treatment assignments. The treatment assignment was concealed from the doctor and the patient by using 2 series of sealed, progressively numbered envelopes for men and women.

Dietary regimens

No variation in normal dietary habits was prescribed to the control patients except that beverage consumption amounted to 2 L/d in the cold season (October–March) and 3 L/d in the warm season (April–September); the water that was consumed had a low sodium and calcium content (7 mg Na/L, 15.9 mg Ca/L,

6.3 mg Mg/L, 4.4 mg K/L, 81.7 mg HCO₃⁻/L, 6 mg SO₄⁻/L, 13.9 mg Cl/L, 7 mg NO₄⁻/L, 12.8 mg SiO₂/L, pH 6.8; Fiuggi water; Fiuggi-Sangemini, Frosinone, Italy).

In addition to the water therapy, patients allocated to the low-salt diet were recommended to eliminate the intake of kitchen salt (including salt added to foods and salt used for cooking) and to strictly limit their consumption of food with a high salt content, as specified on the instruction sheet given to them after detailed explanations and information were provided to them by a member of our team who specialized in food science. To improve food palatability, in place of kitchen salt, the patients were advised to use various herbs and spices, as detailed on the instruction sheet. Another dietary recommendation concerned the intake of calcium in amounts of 800–1000 mg/d, which was to be achieved through the consumption of milk, yogurt, and cheeses with a low salt content. Apart from these restrictions, the diet was free. In addition to detailed oral explanations, all patients in this group were given a sheet with written instructions containing dietary recommendations (see Supplemental Appendix 1 under “Supplemental data” in the online issue) accompanied by a sheet containing a list of hidden sources of salt (see Supplemental Appendix 2 under “Supplemental data” in the online issue).

Data collection and follow-up

During the screening period, all patients were screened according to the consolidated diagnostic protocol, which was designed to ascertain whether or not they were affected by idiopathic calcium-oxalate stone disease.

One of these tests consisted of the determination of urinary stone risk variables in the 24-h urine samples collected while on an ad libitum diet according to previously published methods (18, 19).

Once the diagnosis of idiopathic calcium stone disease was established, compliance with the inclusion criteria was checked, and the informed consent form was signed, the patients were randomly assigned to 1 of the 2 dietary treatments. Agreements were made with each patient concerning the dates when the allocated treatment would start and the final control at the study completion would take place. Each patient received the cellular phone numbers of 2 members of our team so that they could contact us whenever unforeseen problems might occur, especially those regarding compliance with the assigned diet.

Statistical analyses

Stata 10.1 software (2007; StataCorp, College Station, TX) was used for all analyses. We assumed that the baseline daily urinary calcium excretion was, on average, 450 mg in men (20) and 400 mg in women, with an SD of 100 mg for both (20), and that the average sodium chloride intake was ≈200 mmol/d (20). Previous studies (12–14, 16) conducted in hypercalciuric stone-forming patients showed that a reduction in sodium chloride intake of 100 mmol caused, on average, a reduction of ≈100 mg Ca/d. Because the low-salt diet contains ≈60 mmol NaCl, the expected average daily urinary excretion at follow-up should be 310 mg/d in men and 260 mg/d in women, which is close to the upper limit of the normal range (ie, <300 mg in men and <250 mg in women). Therefore, assuming that calcium excretion is approximately normally distributed, about half of male and female subjects on the

low-salt diet should have urinary calcium excretion within the normal range at follow-up. Allowing for a proportion of 25% of patients on the control diet with urinary calcium excretion in the normal range at follow-up, ≈ 100 subjects in each group would achieve a 95% power to declare a statistical significance at a 2-sided α level of 0.05.

Data analyses

All comparisons between treatment groups were based on the intention-to-treat principle. The difference in the proportion of subjects with urinary calcium normalization at follow-up (ie, after 3 mo of dietary intervention), which was the primary endpoint of the trial, was examined by Fisher's exact test. A 2-sided P value < 0.05 was significant. The exact test for effect modification by sex was performed with the Stata program *exlogistic* (StataCorp). The differences in continuous variables at follow-up were examined by analysis of covariance, allowing the adjustment for differences at baseline. Variables were transformed to improve normality, whenever appropriate, with the Stata program *ladder* (StataCorp). Effect modification by sex was tested by using an interaction term between the indicator variables sex and treatment. For all of these analyses, we decided to report nominal P values, although we regarded only those P values < 0.05 as statistically significant after Bonferroni-Holm adjustment for multiple testing. Finally, we performed an analysis, which was not planned for in the initial protocol, to test the hypothesis that the intake of dried meats and hard cheeses, notoriously acid-forming foods, was an important but overlooked source of sodium chloride intake in our study population. To this purpose, we applied factor analysis to generate one factor scored by the regression method and proportional to phosphate, sulfate, and ammonium excretion. We examined the correlation between the score of this new factor and sodium chloride intake in the treatment groups at baseline and the follow-up visit.

RESULTS

As shown in **Figure 1**, the flow of patients was subdivided into enrollment, allocation, follow-up, and analysis. Out of 624 subjects assessed for eligibility, 210 patients who fulfilled the inclusion criteria agreed to participate (150 men and 60 women). Thirteen patients withdrew from the trial: 2 patients assigned to the control diet and 11 patients to the low-salt diet ($P = 0.019$ for the difference in dropout rates). The 2 patients on the control diet refused to undergo the second 24-h urine collection because of work commitments. The 11 patients assigned to the low-salt diet refused to continue the study and to attend the 3-mo follow-up visit, alleging that they could not tolerate the low-salt diet.

The demographic and clinical features of the 2 dietary treatments studied are shown in **Table 1**. Both groups contained relapsing and nonrelapsing stone formers as well as patients who were subjected to procedures for the removal of kidney stones (surgical or otherwise). Mean values for urinary stone risk variables, including body mass index (BMI; in kg/m^2) and arterial blood pressure measured at baseline and the follow-up visit, are shown in **Table 2**.

On average, patients on the low-sodium diet showed a 70% marked reduction in urinary sodium and chloride from baseline to

the follow-up visit (sodium: 228 compared with 68 mmol Na/d; chloride: 231 compared with 74 mmol Cl/d). On the basis of these urinary data, the spontaneous mean baseline intake of sodium chloride in these patients was ≈ 13 g/d, and it had reduced to ≈ 4 g/d at the follow-up visit. In contrast, in patients on the control diet treated with water therapy only, there was only a slight and nonsignificant reduction in sodium chloride excretion.

With the use of factor analysis, we generated a single variate (factor) with a score proportional to phosphate, sulfate, and ammonium excretion, which reflected the intake of foods such as dried meats and hard cheeses. At baseline there was a high correlation between the factor and sodium excretion ($r = 0.39$, $P < 0.001$) with no difference between the 2 groups. At follow-up, the mean of the factor was lower in patients on the low-salt diet ($P = 0.02$). Moreover, the correlation between the factor and sodium excretion remained significant in the control group ($r = 0.30$, $P = 0.003$) but disappeared in the low-salt group ($r = 0.00$, $P = 0.95$) ($P = 0.036$ for the difference between the 2 correlation coefficients). These analyses proved that foods bringing about an increase in phosphate, sulfate, and ammonium excretion (such as dried meats and hard cheeses) represented an important source of sodium intake in our study population.

From the analysis of the other urinary variables and comparison with analysis of covariance, at the follow-up visit, compared with patients on the control diet, patients on the low-sodium diet had lower urinary calcium (271 compared with 361 mg/d; mean difference: -90 mg/d; 95% CI: -59 , -121 ; $P < 0.001$) and lower oxalate excretion (28 compared with 32 mg/d; mean difference: -4.0 mg/d; 95% CI: -1.4 , -6.6 ; $P < 0.001$). As shown in **Table 2**, there was also a slight difference in urea, phosphorus, uric acid, and BMI, although these differences were not significant after adjustment for multiple testing.

All of these findings did not significantly differ between the 2 sexes (data not shown). In particular, the excretion of calcium in the low-sodium-diet group decreased at follow-up by 38% in men (443 mg/d at baseline compared with 273 mg/d after 3 mo) and by 34% in women (403 mg/d at baseline compared with 266 mg/d after 3 mo). Expressing the reduction in calcium excretion in relation with a sodium reduction of 100 mmol, calcium excretion decreased by ≈ 64 mg/100 mmol Na (90 mg/140 mmol) in men and women.

At the follow-up visit, 61.9% (60/97) of the patients on the low-salt diet and 34.0% (34/100) of those on the control diet had urinary calcium excretion within the normal range (difference: +27.9%; 95% CI: +14.4%, +41.3%; $P < 0.001$).

DISCUSSION

This results of this trial show, perhaps for the first time to our knowledge, that a reduction in dietary sodium chloride intake maintained over a prolonged period of time markedly improved idiopathic hypercalciuria in patients with calcium stone disease, bringing about its normalization in a substantial proportion of them.

This effect had only been observed in short-term trials (a few days) and without a control group (12–14, 16). In a previous study by Borghi et al (20), a diet containing normal calcium, low protein, low salt, and high potassium induced a decrease in calcium excretion in stone formers with idiopathic hypercalciuria.

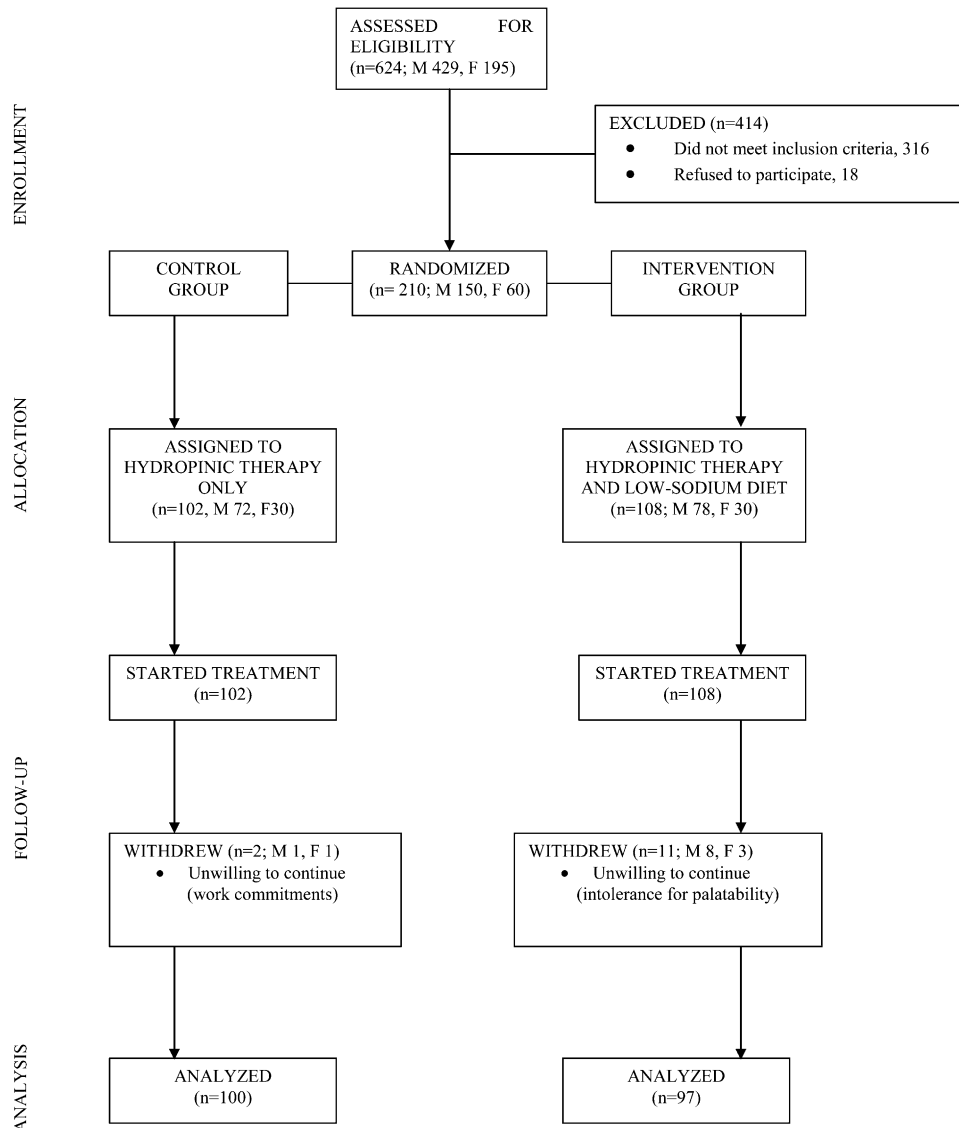


FIGURE 1. Flow of participants.

However, the trial was carried out in men only and did not distinguish the effect of the salt reduction from those effects due to the other dietary changes.

In the current study, we endeavored to assess whether the reduction of salt by itself might normalize idiopathic hypercalciuria. To this purpose, we chose a simple approach, which was easily applicable in a clinical practice. Patients assigned to the control diet had to adhere to water therapy only—ie, they had to simply drink water having a low sodium content, a treatment that had already proved efficacious in preventing stone relapses (18)—whereas those assigned to the low-salt diet, in addition to the water treatment, had to reduce their sodium chloride intake as much as possible through the elimination of kitchen salt added to foods and through the strict limitation in the intake of foods containing high quantities of salt.

A number of limitations should be taken into account when evaluating the findings of this study. First, patients were selected on the basis of their motivation to comply with the dietary regimen assigned. However, 11 patients on the low-sodium diet

(10%) refused to continue the study due to the low palatability of the diet. The rate of dropouts due to this reason was virtually identical to that reported in the previous study by Borghi et al (20) in which the effects of a low-salt, low-calcium, and low-protein diet were tested. Therefore, ≈ 1 in every 10 patients refused to comply with our low-salt diet. Second, because of our inclusion criteria, the study findings are applicable only to patients used to a diet having a high salt content (averaging as much as 13 g/d). However, the sodium intake shown in our study population is not unusual for Western populations (7). Third, ideally, two 24-h urine samples should have been collected at baseline and again at the end of the follow-up, given the known substantial within-person variability. However, the large sample size of the present study might have compensated for this source of random variation. Finally, patients on the control diet were not given any specific instructions regarding the need to maintain a normal calcium intake. Therefore, the difference between the control diet and the low-sodium diet might not be limited to sodium intake alone. However, had we provided specific instructions

TABLE 1
Baseline demographic and clinical characteristics of each treatment group

Characteristic	Control diet (n = 102)	Low-sodium diet (n = 108)
Age (y)	40 ± 10 ¹	39 ± 9
Body weight (kg)	74 ± 12	74 ± 12
Height (cm)	171 ± 9	172 ± 9
Body mass index (kg/m ²)	25 ± 3	25 ± 3
Men [n (%)]	72 (71)	78 (72)
Recurrent patients [n (%)]	70 (69)	67 (62)
Patients with surgical procedures [n (%)] ²	38 (37)	43 (40)
24-h Creatinine clearance (mL/min)	123 ± 28	125 ± 24

¹ Crude (ie, unadjusted for baseline differences) mean ± SD (all such values).

² At least one urologic procedure for removal of kidney stones (ie, extracorporeal shock-wave lithotripsy, percutaneous nephrolithotomy, endourologic techniques, and open surgery) before enrollment in the trial.

regarding calcium intake to patients on the control diet, we would have probably substantially changed their sodium intake altogether.

The reduction of 100 mmol urinary Na (corresponding to a reduction in intake of 5.8 g/d) was accompanied at follow-up by a reduction in urinary calcium of about 64 mg/d in men and women, with a net gain of ≈30% of patients achieving normal calciuria.

In previous studies (9–17), it was calculated that an increase of 100 mmol Na brought about an increase of 40 mg urinary Ca in normal adults and 80–120 mg Ca in hypercalciuric stone formers. We believe that those studies slightly overestimated the effect of salt intake on calciuria because they did not compare their findings with a control group. In fact, if we do not take into consideration the control group, our study would exactly confirm

the previous observation that a decrease of ≈100 mmol urinary Na brings about a decrease of 100 mg calciuria, whereas on the basis of the comparison with the control group, this effect decreased by about one-third. This is easily explainable because a study with a control group eliminates spurious effects such as the regression toward the mean phenomenon or other extraneous, perhaps unmeasurable, factors that can be shared by every patient enrolled in the trial.

Even though the previously described studies cannot be not directly compared with ours, it seems that the hypercalciuric patients in our study, or at least some of them, were particularly sensitive to changes in salt intake. Our data confirmed that the decrease in sodium chloride intake was associated with a fairly generalized reduction in calciuria, but this effect appeared to be substantial, able to reach the complete normalization, in some patients only. Such a response suggests that there are salt-dependent and salt-independent hypercalciuric subjects as surmised by others (16).

To explain the calcium-reducing effect of the low-sodium diet, various possible mechanisms need to be considered. First, it is well known that in the distal segments of the renal tubule, sodium, and calcium compete for reabsorption; therefore, as the quantity of sodium arriving at the distal tubule increases, the calcium excretion also increases (21). Another mechanism might involve the inhibitory effect of plasma volume expansion on sodium and calcium reabsorption in the proximal tubule and in Henle's loop (21). The reduction in the intake of sodium chloride, especially in patients used to a high consumption of salt, might bring about a decrease in the circulating volume and, thereby, in calcium excretion. A third mechanism might involve the acid–base balance. As shown in a recent study (22), an excess of sodium chloride intake can promote a chronic state of subclinical metabolic acidosis leading to a release of bone calcium. A 3-month

TABLE 2
Baseline and follow-up (3 mo) urinary measurements in each treatment group¹

	Baseline		At 3 mo		P value ²
	Control diet (n = 102)	Low-sodium diet (n = 108)	Control diet (n = 100)	Low-sodium diet (n = 97)	
Volume (mL/d)	1754 ± 787	1862 ± 678	2145 ± 712	2213 ± 843	0.936
Creatinine (mg/d)	1677 ± 433	1745 ± 404	1605 ± 376	1546 ± 385	0.051
Urea (g/d)	27 ± 9	28 ± 8	25 ± 6	23 ± 8	0.037
Sodium (mmol/d)	220 ± 63	228 ± 57	200 ± 61	68 ± 43	<0.001
Chloride (mmol/d)	216 ± 69	231 ± 58	197 ± 70	74 ± 62	<0.001
Potassium (mmol/d)	59 ± 19	59 ± 18	59 ± 19	58 ± 19	0.557
Calcium (mg/d)	418 ± 100	432 ± 96	361 ± 129	271 ± 86	<0.001
Phosphorus (mg/d)	998 ± 316	969 ± 272	893 ± 245	801 ± 237	0.013
Magnesium (mg/d)	115 ± 40	111 ± 31	102 ± 35	95 ± 28	0.278
Uric acid (mg/d)	658 ± 212	683 ± 201	580 ± 168	539 ± 153	0.030
Citrate (mg/d)	624 ± 275	629 ± 250	632 ± 251	620 ± 252	0.644
Oxalate (mg/d)	33 ± 13	33 ± 10	32 ± 10	28 ± 8	0.001
Sulfate (mmol/d)	24 ± 7	24 ± 7	22 ± 7	21 ± 6	0.189
Ammonium (mmol/d)	41 ± 13	42 ± 13	39 ± 11	36 ± 11	0.062
pH (24 h)	5.99 ± 0.47	6.04 ± 0.44	6.01 ± 0.47	6.01 ± 0.42	0.854
BMI (kg/m ²)	25 ± 3	25 ± 3	25 ± 3	24 ± 3	0.049
Systolic BP (mm Hg)	129 ± 13	128 ± 10	126 ± 8	125 ± 9	0.144
Diastolic BP (mm Hg)	83 ± 9	82 ± 8	82 ± 6	81 ± 5	0.240

¹ All values are crude (ie, unadjusted for baseline differences) means ± SDs. BP, blood pressure.

² Derived by using ANCOVA; differences between group means at follow-up were tested with adjustment for differences at baseline.

period on a low-sodium diet, such as that accomplished in the present study, might have modified this acid-base imbalance leading to a reduction, also by this route, of the urinary excretion of calcium. Finally, a fourth element has to be considered. The low-salt diet brought about, together with the described urinary changes, a slight decrease in BMI associated with changes in some urinary markers of protein intake (eg, urea, phosphorus, and uric acid), although these differences were no longer significant after adjustment for multiple testing. This effect led us to think that the low-sodium diet, which involved the elimination of added salt and a strict restriction of foods containing a high salt content, might have brought about wider, but subtle, dietary changes, such as a decrease in caloric and protein intakes. This hypothesis appears to be plausible considering that adding pure salt has no effect on the urinary excretion of the aforementioned elements (ie, urea, phosphorus, uric acid) (23).

The reduction in salt intake might have reduced the oxalate intestinal absorption accounting for the decrease in urinary oxalate. It is well known that the greatest proportion of oxalate is absorbed in the distal portion of the intestine and highly depends on the quantity of calcium present in this intestinal segment: if more calcium is present in this area, it binds to the oxalate to form poorly absorbable calcium oxalate (24). The reduction in calciuria caused by the reduced intake of salt might lead, through a homeostatic mechanism, to a reduction in the absorption of calcium in the more proximal portions of the intestine, leaving a greater proportion of it more available at the distal level to form greater quantities of nonabsorbable calcium oxalate.

In conclusion, the results of this study show that a low-salt diet, accomplished by eliminating added salt and reducing foods with a high salt content, corrected idiopathic hypercalciuria in $\approx 30\%$ of the cases. A low-salt diet also seemed to have a positive effect on other urinary stone risk factors. In more general terms, the results of this study provide further motivation for reducing the excessive consumption of salt, as already implemented in some countries (25, 26).

The authors' responsibilities were as follows—AN and LB: study design, data collection, and manuscript preparation; TM: supervision of data collection and data entry; BP and FA: data collection; AG: laboratory procedures; GV, LS, and GG: supervision of study design and manuscript preparation; and UM: data analysis and manuscript preparation. None of the authors had any potential conflicts of interest.

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