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COMPARISON OF TWO DIETS FOR THE PREVENTION OF RECURRENT STONES IN IDIOPATHIC HYPERCALCIURIA

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ABSTRACT

Background A low-calcium diet is recommended to prevent recurrent stones in patients with idiopathic hypercalciuria, yet long-term data on the efficacy of a low-calcium diet are lacking. Recently, the efficacy of a low-calcium diet has been questioned, and greater emphasis has been placed on reducing the intake of animal protein and salt, but again, long-term data are unavailable.

Methods We conducted a five-year randomized trial comparing the effect of two diets in 120 men with recurrent calcium oxalate stones and hypercalciuria. Sixty men were assigned to a diet containing a normal amount of calcium (30 mmol per day) but reduced amounts of animal protein (52 g per day) and salt (50 mmol of sodium chloride per day); the other 60 men were assigned to the traditional low-calcium diet, which contained 10 mmol of calcium per day.

Results At five years, 12 of the 60 men on the normal-calcium, low-animal-protein, low-salt diet and 23 of the 60 men on the low-calcium diet had had relapses. The unadjusted relative risk of a recurrence for the group on the first diet, as compared with the group on the second diet, was 0.49 (95 percent confidence interval, 0.24 to 0.98; $P=0.04$). During follow-up, urinary calcium levels dropped significantly in both groups by approximately 170 mg per day (4.2 mmol per day). However, urinary oxalate excretion increased in the men on the low-calcium diet (by an average of 5.4 mg per day [60 μ mol per day]) but decreased in those on the normal-calcium, low-animal-protein, low-salt diet (by an average of 7.2 mg per day [80 μ mol per day]).

Conclusions In men with recurrent calcium oxalate stones and hypercalciuria, restricted intake of animal protein and salt, combined with a normal calcium intake, provides greater protection than the traditional low-calcium diet. (N Engl J Med 2002;346:77-84.)

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IDIOPATHIC hypercalciuria is an important¹ and common² risk factor for the formation of stones, and uncontrolled hypercalciuria is a cause of recurrences.³ Thiazides can reduce urinary calcium excretion,⁴ but since calcium excretion depends in part on diet,⁵ initial attempts to decrease hypercalciuria should involve dietary modification. Since most patients with hypercalciuria have intestinal hyperabsorption of calcium,⁶ it is common clinical practice to recommend a low-calcium diet. However, there are no long-term data on the efficacy of this approach.

Short-term studies have shown that a low calcium intake significantly reduces urinary calcium excretion but can cause a deficiency of calcium and an increase in urinary oxalate.^{7,8} Curhan et al.⁹ reported that among men without a history of nephrolithiasis, those with a high intake of calcium (>26.2 mmol per day) had a 34 percent lower risk of stone formation than did those with a low calcium intake (<15.1 mmol per day), a finding that makes the protective efficacy of a low-calcium diet doubtful.¹⁰ This observation was later confirmed in women.¹¹ Moreover, studies have shown that animal protein¹²⁻¹⁶ and salt¹⁷⁻²² also have a considerable influence on calcium excretion.

We compared the efficacy of the traditional low-calcium diet with that of a diet containing a normal amount of calcium but reduced amounts of animal protein and salt. Increased consumption of water was recommended with both regimens.

METHODS

Study Population

Men referred to our outpatient department were eligible for the study if they met all the following criteria: idiopathic hypercalci-

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uria (urinary calcium excretion, >300 mg per day [7.5 mmol per day]) on an unrestricted diet, recurrent formation of calcium oxalate stones (at least two documented events — that is, colic episodes with expulsion of stones or radiographic evidence of retained stones), no known condition that is commonly associated with calcium nephrolithiasis (e.g., primary hyperparathyroidism, primary hyperoxaluria, enteric hyperoxaluria, bowel resection, inflammatory bowel disease, renal tubular acidosis, sarcoidosis, or sponge kidney), no previous visit to a stone disease center, no current treatment for the prevention of recurrent stones except for the advice to increase water intake, and residence in the area of Parma, Italy.

Eligibility was determined after a run-in period of two to three months,^{23,24} during which the cause of stone formation was determined. Each patient was seen at least three times during the run-in period. Ultrasound and radiologic studies and serum measurements were performed, as well as urinalysis, culture, and chemical measurements in two 24-hour urine specimens, while the men remained on an unrestricted diet. All patients were clinically evaluated by one of us.

Eligible men were asked whether they were willing to comply with the assigned dietary regimen for at least five years. They received detailed information about the risk factors for urinary stones, with a focus on the role of calcium, animal protein, and salt in the diet. They were informed that the purpose of the trial was to determine which of the two diets under study was more effective.

Randomization

After the run-in period, the men who had given written informed consent were randomly assigned to one diet or the other. The treating physicians assigned the men to the dietary regimens on the basis of a random-number sequence (an odd number for the low-calcium diet and an even number for the diet containing a normal amount of calcium and reduced amounts of animal protein and salt). The sequence was generated by one of us, who enclosed the numbers indicating the assignments in sealed, numbered envelopes.

Dietary Regimens

The men assigned to the low-calcium diet were instructed to avoid milk, yogurt, and cheese so that calcium intake would be reduced to approximately 10 mmol per day. As part of our routine clinical practice, we also advised the men to avoid consuming large amounts of oxalate-rich foods (e.g., walnuts, spinach, rhubarb, parsley, and chocolate).

The other dietary regimen was more complex and specific (Table 1). The men assigned to this regimen were given written explanations and detailed information designed to help them comply with the regimen. As compared with the typical diet in our region,²⁵ this diet was low in protein, particularly that of animal origin, and low in salt, with a normal-to-high intake of calcium. We also advised the men on this diet to avoid consuming large amounts of foods that are rich in oxalate. Patients who found the diet to be too low in calories were instructed to increase their consumption of bread, pasta, vegetables, and fruit rather than their consumption of meat or fish. Both diets included 2 liters of water per day in cold weather and 3 liters per day in warm weather. Moderate consumption of wine, beer, carbonated beverages, and coffee was allowed. Further information on the dietary instructions is available as Supplementary Appendix 1 with the full text of this article at <http://www.nejm.org>.

Data Collection and Follow-up

Twenty-four-hour urine specimens were obtained at base line (with values documented as the average of the two sets of measurements performed before randomization), one week after randomization, and at yearly intervals during the five years of the study. Urinary volume was measured as a marker of liquid consumption, sodium (measured by atomic-absorption spectrophotometry) as a

TABLE 1. COMPOSITION OF THE NORMAL-CALCIUM, LOW-PROTEIN, LOW-SALT DIET.*

DAILY INTAKE	VALUE
Total calories (kcal)	2540
Total protein (g)	93 (372 kcal, or approximately 15% of total calories)
From meat or fish	21
From milk and derivatives	31
From bread, pasta, and vegetables	41
Lipids (g)	93 (837 kcal, or approximately 33% of total calories)
Carbohydrates (g)	333 (1332 kcal, or approximately 52% of total calories)
Fiber (g)	40
Sodium chloride (mmol)	50
Potassium (mmol)	120
Calcium (mmol)	30
Phosphorus (mmol)	48.8
Magnesium (mmol)	14.5
Oxalate (mmol)	Approximately 2.2
Water in foods (ml)	1550

*The data were obtained from the composition tables issued in 1989 by the Italian National Institute for Nutrition. The values are based on direct chemical analyses of the foods available in Italian markets.

marker of salt intake, urea (measured by the urease method) as a marker of total protein intake, and sulfate (measured by ion chromatography) as a marker of animal-protein intake. Calcium excretion was measured by atomic-absorption spectrophotometry, oxalate excretion by ion chromatography, and creatinine excretion by the Jaffe reaction. The urine specimen obtained one week after randomization was analyzed to check compliance with the dietary regimen. The ratio of creatinine excretion to body weight was used to verify that the urine had been collected correctly.

The relative calcium oxalate saturation was measured with the use of the Equil computer program at base line and after the first week of the diet. Subsequently, the relative calcium oxalate saturation was estimated according to a formula obtained by regression analysis with the use of data from previous studies.^{23,24}

Outcome Measures

The primary outcome measure was the time to the first recurrence of a symptomatic renal stone or the presence of a radiographically identified stone (see below). In the event of a recurrence, the treatment was considered to have failed, and the patient was withdrawn from the trial. If there were no recurrences, patients were followed until the fifth annual visit (month 60). Patients who required treatment with thiazides or allopurinol for conditions such as hypertension or gout were withdrawn from the trial.

Recurrences were considered to be either silent or symptomatic. Silent recurrences were diagnosed on the basis of renal ultrasound and abdominal flat-plate examinations performed at yearly intervals. If renal stones were detected, stratigraphy (thin-plane radiography) was also performed. The imaging studies were performed by a central radiologic service, and the radiologist had no knowledge of the trial or the group assignments. A recurrence was classified as silent

if a previously unreported stone was detected in the absence of symptoms. A symptomatic recurrence was defined as typical renal colic, an episode of hematuria, or the expulsion or removal of a previously undiscovered stone. If a symptomatic recurrence was documented on the basis of renal colic or hematuria, the recurrence had to be confirmed radiographically.

Secondary outcome measures included changes in calcium and oxalate excretion, the calcium oxalate product, and the relative calcium oxalate saturation.

Statistical Analysis

The analysis was based on the intention-to-treat principle. We used Kaplan–Meier analyses to determine the cumulative incidence of recurrent stones, and we used Cox proportional-hazards regression to determine the crude and adjusted relative risks of recurrence. Analyses were performed with Stata software (version 7, Stata, College Station, Tex.). Before the study, we estimated that an overall sample of 120 men was required for 80 percent power at a significance level of 0.05 to detect a difference of 25 to 50 percent in the risk of a recurrence between the two study groups, using a two-sided log-rank test.

Although we had not previously planned to do so, we adjusted the relative risk of a recurrence for clinical characteristics known to be strong predictors of the likelihood of a recurrence²⁶ — namely, the total number of stones formed previously and the number of episodes of renal colic in the previous year. In addition, we tried to determine whether the effects of dietary treatments varied ac-

ording to the severity of the disease. To this end, we established a subgroup of men at highest risk — those in the highest decile for either of the two predictors of a recurrence. The men at highest risk (23 of 120, or 19.2 percent) were those with a history of five or more episodes of colic in the year before randomization, 10 or more stones formed (as documented on the basis of expulsion or radiography) before randomization, or both. The highest-risk men tended to have higher base-line urinary indexes, such as higher levels of oxalate, calcium, sulfate, sodium, and urea, than the other men, though they also had higher urinary volume. We then performed an analysis with a Cox model that included an interaction term for dietary group and the highest-risk category.

For the analysis of the urinary indexes, we compared the two groups with respect to the absolute change from the base-line value at each time point. These comparisons were carried out with use of the Mann–Whitney test. Base-line continuous variables were compared with use of the Mann–Whitney test and Student’s t-test whenever appropriate; categorical variables were compared with use of Fisher’s exact test.

All data are expressed as means ±SD. A P value of less than 0.05 was considered to indicate statistical significance. All reported P values are two-sided.

RESULTS

A total of 120 men were enrolled in the study between June 1993 and December 1994, and 60 men

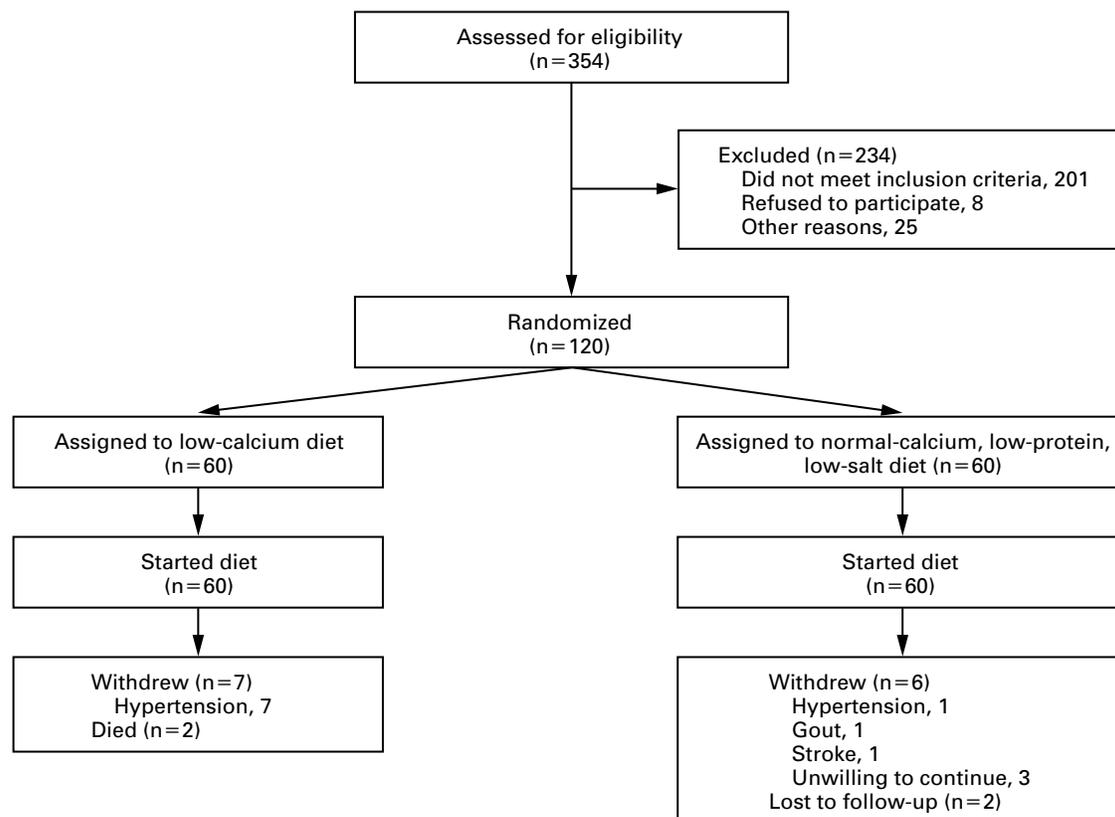


Figure 1. Enrollment, Randomization, and Follow-up.

Both deaths were accidental. The two men who were lost to follow-up moved to another area.

were assigned to each diet. Seventeen men did not complete the study (Fig. 1). Of these 17, 3 assigned to the normal-calcium, low-protein, low-salt diet withdrew because they did not want to continue with the diet; 7 assigned to the low-calcium diet withdrew because of hypertension, a possible adverse effect of low calcium intake.²⁷ The base-line demographic and clinical characteristics of the two groups were similar (Table 2).

Twenty-three of the 60 men on the low-calcium diet and 12 of the 60 on the normal-calcium, low-protein, low-salt diet had recurrences. The cumulative incidence of recurrent stones in the two groups is shown in Figure 2. The relative risk of a recurrence among the men in the normal-calcium, low-protein, low-salt group, as compared with the men in the low-calcium group, was 0.49 (95 percent confidence interval, 0.24 to 0.98; $P=0.04$). After adjustment for the total number of stones formed before randomization and the number of colic episodes in the year before randomization, the relative risk of a recurrence was 0.37 (95 percent confidence interval, 0.18 to 0.78; $P=0.006$). Further adjustment for the remaining base-line characteristics did not change the estimate of the relative risk (data not shown). The incidence of recurrent stones differed significantly between the two groups only late in the follow-up period (Fig. 2). As the stratified analysis in Figure 3 shows, this delayed effect was due to early recurrences in the highest-risk patients, regardless of the diet to which they were assigned.

Table 3 shows the values for the urinary variables throughout the follow-up period. The 24-hour urinary volume increased to a similar extent in the two groups. As expected, urinary excretion of sodium, urea nitrogen, and sulfate did not change with the low-calcium diet, whereas all three indexes decreased with the normal-calcium, low-protein, low-salt diet. The decrease in these indexes reflects dietary compliance, which was excellent in the first week and still fairly good, although somewhat reduced, during follow-up.

As shown in Table 3, calcium excretion decreased with both diets (by approximately 170 mg per day [4.2 mmol per day]). The calcium oxalate product and the relative calcium oxalate saturation decreased with both diets, although the reduction was greater with the normal-calcium, low-protein, low-salt diet. The main difference between the two diets was oxalate excretion, which increased with the low-calcium diet (by approximately 5.4 mg per day [60 μmol per day]) but decreased with the normal-calcium, low-protein, low-salt diet (by approximately 7.2 mg per day [80 μmol per day]). There were no differences in dietary compliance between the men who had recurrent stones and those who did not, irrespective of the diet.

TABLE 2. BASE-LINE CHARACTERISTICS IN THE TWO STUDY GROUPS.*

CHARACTERISTIC	DIET	
	LOW CALCIUM (N=60)	NORMAL CALCIUM, LOW ANIMAL PROTEIN, AND LOW SALT (N=60)
Age — yr	45.4±10.9	44.8±9.2
Body weight — kg	76.5±8.7	79.3±9.4
Blood pressure — mm Hg		
Systolic	132±13	132±16
Diastolic	81±7	83±11
Family history of stones — no. of patients (%)	24 (40)	26 (43)
Total stones — no.	5.1±5.4	5.6±7.7
Colic episodes in previous year — no.	2.4±1.5	2.6±2.3
Lithotripsy or other procedures required — no. of patients (%)	23 (38)	24 (40)
At highest risk — no. of patients (%)†	9 (15)	14 (23)
Retained stone — no. of patients (%)	19 (32)	13 (22)
Serum creatinine — μmol /liter	86.7±6.9	87.6±6.9
Serum calcium — mmol/liter	2.32±0.08	2.35±0.08
Serum phosphorus — mmol/liter	1.10±0.15	1.06±0.15
Creatinine clearance — ml/min	123±16	128±17
Urinary creatinine — mmol/day	15.4±2.67	16.2±2.32
Urinary volume — ml/day	1755±844	1852±643
Urinary sodium — mmol/day	227±59	241±67
Urinary urea nitrogen — mmol/day	505±116	510±139
Urinary sulfate — mmol/day	27±7	28±8
Urinary calcium — mmol/day	11.0±2.5	11.5±2.5
Urinary oxalate — μmol /day‡	367±136	411±132
Urinary calcium oxalate Product — $\text{mol}\cdot 10^{-6}$ /liter	2.07±2.11	1.82±1.26
Relative saturation§	10.1±5.5	9.6±4.2

*Plus-minus values are means \pm SD. There were no significant differences between the two groups. To convert the values for creatinine to grams per day, divide by 8.8. To convert the values for calcium to milligrams per day, divide by 0.02495. To convert the values for urea nitrogen to grams per day, divide by 35.70. To convert the values for oxalate to milligrams per day, divide by 11.11. Each urinary value is the mean of the two measurements performed while the patients were on an unrestricted diet.

†Patients at highest risk were those with a history of five or more colic episodes in the previous year, a total of 10 or more stones, or both.

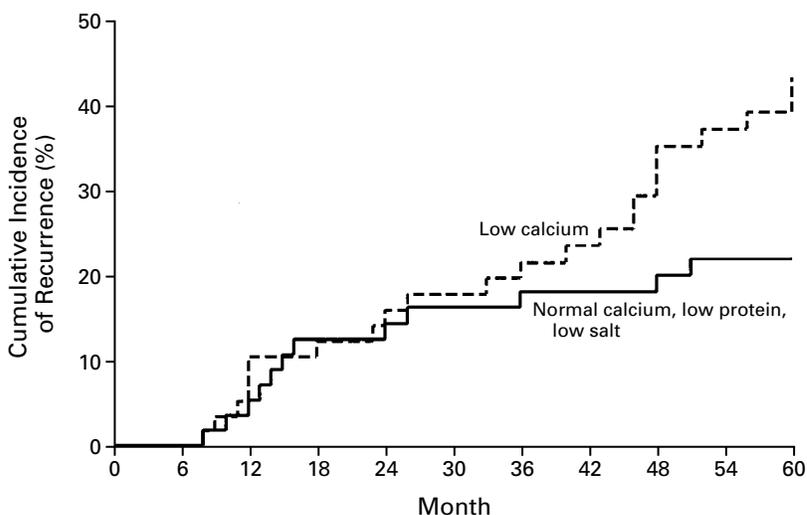
‡In our laboratory, the normal range of oxalate excretion in healthy men is 80 to 500 μmol per day; a subgroup of the patients had mild hyperoxaluria (13 percent on the low-calcium diet and 23 percent on the normal-calcium, low-animal-protein, low-salt diet).

§The relative saturation (expressed as a ratio) was measured with the use of the Equil program.

DISCUSSION

This study shows that a diet with a normal amount of calcium but with reduced amounts of animal protein and salt is more effective than the traditional low-calcium diet in reducing the risk of recurrent stones in men with idiopathic hypercalciuria. The difference appears to be due to the different effects of the two diets on oxalate excretion.

Studies extending short-term investigations⁸ have



No. AT RISK		0	6	12	18	24	30	36	42	48	54	60
Low calcium		60	59	51	49	46	44	42	39	33	31	28
Normal calcium, low protein, low salt		60	57	53	47	46	45	44	43	41	40	40

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Recurrent Stones, According to the Assigned Diet.

The relative risk of a recurrence in the group assigned to the normal-calcium, low-protein, low-salt diet, as compared with the group assigned to the low-calcium diet, was 0.49 (95 percent confidence interval, 0.24 to 0.98; P=0.04).

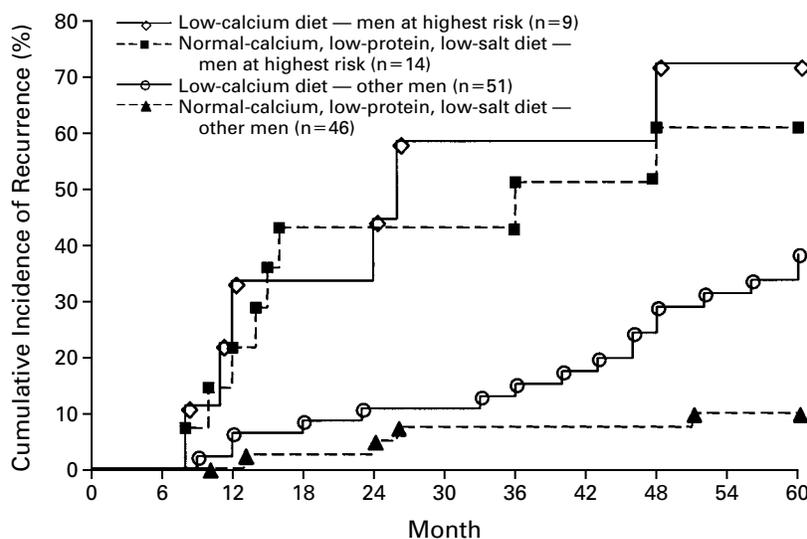


Figure 3. Kaplan–Meier Estimates of the Cumulative Incidence of Recurrent Stones, According to the Risk of Recurrence at Base Line.

The men at highest risk were those with five or more colic episodes in the year before randomization, 10 or more stones before randomization, or both. Among the men who were at highest risk for recurrent stones, the relative risk of a recurrence was 0.81 (95 percent confidence interval, 0.28 to 2.35) for the men on the normal-calcium, low-protein, low-salt diet, as compared with those on the low-calcium diet. Among all the other men, the relative risk of a recurrence was 0.23 (95 percent confidence interval, 0.08 to 0.67) for the men on the normal-calcium, low-protein, low-salt diet. The relative risk of a recurrence did not differ significantly between the two subgroups of men (P=0.09).

TABLE 3. URINARY VARIABLES AT BASE LINE AND DURING TREATMENT.*

URINARY VARIABLE	BASE LINE	1 WEEK	1 YEAR	2 YEARS	3 YEARS	4 YEARS	5 YEARS
Low-calcium diet							
No. of men	60	60	51	46	42	33	28
Volume (ml/day)	1755±844	2025±1089	1905±713	1980±845	1947±667	2200±672	2187±537
Sodium (mmol/day)	227±59	215±50	210±55	209±59	205±64	212±48	201±42
Urea (mmol/day)	505±116	520±132	527±164	535±156	505±142	497±172	490±122
Sulfate (mmol/day)	27±7	27±9	26±8	26±8	27±7	27±7	27±4
Calcium (mmol/day)	11.0±2.5	8.3±3.4	7.6±2.9	7.6±2.9	7.0±3.4	6.3±2.9	6.2±1.2
Oxalate (μmol/day)	367±136	422±148	422±144	411±155	422±144	433±136	411±121
Calcium oxalate							
Product (mol·10 ⁻⁶ /liter)	2.07±2.11	1.53±1.58	1.25±1.17	1.11±0.86	1.16±1.25	0.65±0.38	0.63±0.43
Relative saturation†	10.1±5.5	8.1±5.3	7.3±4.3	6.8±3.7	6.7±4.5	4.8±2.2	4.7±2.2
Normal-calcium, low-protein, low-salt diet							
No. of men	60	60	53	46	44	41	40
Volume (ml/day)	1852±643	2202±798	2095±623	2134±653	2128±520	2318±525	2296±526
Sodium (mmol/day)	241±67	51±41‡	130±85‡	129±101‡	127±66‡	110±50‡	123±47‡
Urea (mmol/day)	510±139	402±116‡	433±95§	423±102‡	447±113	453±128	453±114
Sulfate (mmol/day)	28±8	22±5‡	24±7§	25±7	25±6	24±5§	24±5§
Calcium (mmol/day)	11.5±2.5	6.1±2.2‡	7.3±2.5	7.1±2.2	6.6±2.4	6.4±1.5	5.9±2.4
Oxalate (μmol/day)	411±132	322±91‡	344±92‡	322±86‡	333±106‡	333±79‡	333±82‡
Calcium oxalate							
Product (mol·10 ⁻⁶ /liter)	1.82±1.26	0.53±0.43‡	0.70±0.48¶	0.64±0.44	0.63±0.77	0.46±0.28	0.43±0.27
Relative saturation†	9.6±4.2	4.0±2.4‡	5.1±2.5¶	4.7±2.4§	4.5±2.9§	3.7±1.8	3.5±1.8§

*Plus-minus values are means ±SD. To convert the values for creatinine to grams per day, divide by 8.8. To convert the values for calcium to milligrams per day, divide by 0.02495. To convert the values for urea to grams per day, divide by 35.70. To convert the values for oxalate to milligrams per day, divide by 11.11.

†The relative saturation (expressed as a ratio) was measured with the use of the Equil program at base line and week 1, with subsequent measurements performed according to a formula obtained by regression analysis with the use of data from previous studies.^{23,24}

‡P<0.001 for the absolute change from the base-line value as compared with the absolute change in the low-calcium group.

§P<0.05 for the absolute change from the base-line value as compared with the absolute change in the low-calcium group.

¶P<0.01 for the absolute change from the base-line value as compared with the absolute change in the low-calcium group.

shown that a low-calcium diet has long-term efficacy in reducing calcium excretion. However, this diet may cause an increase in urinary oxalate excretion through increased intestinal absorption, resulting from the low level of calcium available to form a complex with oxalate in the intestinal lumen.^{28,29} In terms of saturation, the increase in oxalate tends to be offset by the reduction in calcium, but the concurrent increase in urinary volume causes a substantial reduction of the calcium oxalate molar product and, hence, of the relative calcium oxalate saturation.

We found that a diet with a normal amount of calcium but reduced amounts of animal protein and salt resulted in a reduction in calcium excretion that was, on the whole, equivalent to that associated with a low-calcium diet. Indeed, after the first week of treatment, the drop in urinary calcium excretion was more marked with this diet than with the low-calcium diet. Subsequently, this difference tended to disappear, probably because of a partial reduction in compliance. The decrease in urinary calcium excretion, despite normal calcium intake, is probably the consequence of the

combined tubular action of the decreased intake of salt and animal protein, a phenomenon previously documented in short-term studies.¹²⁻²²

The other important result of the normal-calcium, low-protein, low-salt diet was the consistent reduction in urinary oxalate excretion. The explanation for the reduction in oxalate excretion with the normal-calcium diet is the converse of the explanation for its increase with the low-calcium diet. With the normal-calcium diet, more calcium is available in the intestinal lumen to form a complex with oxalate, thus reducing its absorption — a phenomenon reported in short-term studies.^{30,31} In addition, the reduced intake of protein may lower the endogenous synthesis of oxalate.³²

The normal-calcium, low-protein, low-salt diet decreases urinary excretion of both calcium and oxalate, which in combination with an increase in urinary volume causes a marked reduction in the calcium oxalate molar product and in the relative calcium oxalate saturation. These effects may explain the 50 percent reduction in the risk of a recurrence among the men

assigned to this diet, as compared with those assigned to the low-calcium diet. However, this advantage was evident only after several years of follow-up. We speculate that the early advantage of the normal-calcium, low-protein, low-salt diet over the low-calcium diet might have been obscured by the enrollment of men who were at high risk for an early recurrence. This interpretation is consistent with that of Parks and Coe,²⁶ who speculated that at the start of treatment, patients at high risk may have stones that are too small to be seen on radiographs but that grow and are later identified as new stones.

Because the patients enrolled in our trial came to us with an explicit request to receive dietary treatment for the prevention of recurrences, it would not have been possible or ethical to include a control group. However, several other studies have included a placebo group or a conservative-treatment group,³³⁻⁴¹ and in all these studies, the risk of a recurrence among patients receiving placebo or conservative treatment was higher than the risk with either diet in our study. Moreover, in studies of the natural history of the disease,⁴²⁻⁴⁴ the risk of a recurrence at five years was approximately 50 percent, which is higher than the risk with either diet in our trial.

While our study was in progress, the results of a trial that examined the protective effect of a diet characterized by low levels of animal protein and high levels of fiber were reported.⁴⁵ The authors concluded that this regimen was not more beneficial than the simple advice to increase the intake of liquids. However, this study differed from ours in several ways. The subjects were patients with a first episode of nephrolithiasis, only 17 percent of whom had hypercalciuria. The dietary prescription did not include restricted salt intake, and there was little control of calcium intake. Moreover, compliance with the diet was poor.

In conclusion, our study suggests that a diet characterized by normal calcium, low animal protein, and low salt levels is more effective than the traditional low-calcium diet for the prevention of recurrent stones in men with idiopathic hypercalciuria. We speculate that this type of diet will be of greatest value when it is started early in the course of the disease.

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