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Randomized Controlled Trial of a Low Animal Protein, High Fiber Diet in the Prevention of Recurrent Calcium Oxalate Kidney Stones

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Low protein diets are commonly prescribed for patients with idiopathic calcium nephrolithiasis, who account for >80% of new diagnoses of kidney stones. This dietary advice is supported by metabolic studies and epidemiologic observational studies but has not been evaluated in a controlled trial. Using 1983–1985 data from three Northern California Kaiser Permanente Medical Centers, the authors randomly assigned 99 persons who had calcium oxalate stones for the first time to a low animal protein, high fiber diet that contained approximately 56–64 g daily of protein, 75 mg daily of purine (primarily from animal protein and legumes), one-fourth cup of wheat bran supplement, and fruits and vegetables. Intervention subjects were also instructed to drink six to eight glasses of liquid daily and to maintain adequate calcium intake from dairy products or calcium supplements. Control subjects were instructed only on fluid intake and adequate calcium intake. Both groups were followed regularly for up to 4.5 years with food frequency questionnaires, serum and urine chemistry analysis, and abdominal radiography; and they were urged to comply with dietary instructions. In the intervention group of 50 subjects, stones recurred in 12 (7.1 per 100 person-years) compared with two (1.2 per 100 person-years) in the control group; both groups received a mean of 3.4 person-years of follow-up ($p = 0.006$). After adjustment for possible confounding effects of age, sex, education, and baseline protein and fluid intake, the relative risk of a recurrent stone in the intervention group was 5.6 (95% confidence interval 1.2–26.1) compared with the control group. The authors conclude that advice to follow a low animal protein, high fiber, high fluid diet has no advantage over advice to increase fluid intake alone. *Am J Epidemiol* 1996; 144:25–33.

calcium oxalate; diet; dietary proteins; kidney calculi; randomized controlled trials

Kidney stones are a common source of morbidity in industrialized countries. The annual incidence of upper urinary tract stones is approximately 1.3/1,000, and the lifetime risk is about 10–12 percent for men and 3–5 percent for women (1, 2). Kidney stones currently lead to 0.4–1.0 of every 1,000 hospital admissions according to population-based studies (1, 3). From 70 to 85 percent of stones are composed primarily of calcium oxalate and have no known cause (4–6).

Patients in whom stones form for the first time are routinely encouraged to increase their fluid intake and to reduce calcium and animal protein in their diet (7, 8). The advice to increase fluid intake is as old as Hippocrates, although no controlled clinical study exists to document effectiveness of increased fluid intake in reducing recurrences. This advice remains a mainstay of the nonspecific treatment of nephrolithiasis (9) and has been supported by experimental evidence showing reduction in the urinary activity product ratio (saturation) of urine among both normal persons and those affected by kidney stones (10). Advice to reduce calcium intake has been given on the basis of calcium content of these stones, but no prospective data support this practice. A recent follow-up study (11) of 45,619 men provided evidence that a high dietary calcium intake actually decreased the risk of symptomatic kidney stones. Theories that relate stone formation to diet, and in particular to dietary animal protein, derive from international ecologic correlations of stone incidence and industrialization (12, 13) and from areas within countries where stones are prevalent (14). In England and Wales, the annual consumption of animal protein determined from a national food survey was strongly correlated with the incidence of hospital diagnosis of kidney stones between 1958 and 1976 (15). Metabolic studies (16–19) have shown that

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increased dietary animal protein increases the urinary excretion of calcium, uric acid, and citrate as well as decreases the ability of urine to inhibit the agglomeration of calcium oxalate crystals in normal subjects. Some case-control studies (20–22) and one cohort study (11) have supported the animal protein hypothesis, although other case-control studies (23–28) have found no difference in animal protein consumption. Increased total dietary fiber has also been linked to a lower risk of stones in metabolic and case-control studies (8, 23) and is believed to work through the intraluminal absorption of minerals and fat and the reduced excretion of calcium and oxalate (23, 29). However, evidence from prospective controlled trials of sufficient length does not support advice to lower protein intake or increase fiber intake to prevent recurrences after a first kidney stone. The need for such trials has recently been emphasized (30).

To improve our understanding of the influence of diet on kidney stones, we used a randomized controlled trial to test the hypothesis that instruction on a low protein, high fiber diet among persons who had calcium oxalate stones for the first time is an effective method to reduce frequency of recurrent stone events.

MATERIALS AND METHODS

Subject selection

Subjects were members of the Kaiser Permanente Medical Care Program who between 1983 and 1985 had a documented single calcium oxalate kidney stone analyzed as ≥65 percent calcium oxalate. Between 1984 and 1985, these subjects were recruited from the San Francisco, Walnut Creek, and Martinez, California, medical centers after approval of their regular physicians. Persons eligible for the trial had to be 20–60 years of age, have had an abdominal radiograph (x-ray film) with negative results within the previous 6 months, speak English, and understand dietary instructions. Persons were excluded if they had a known metabolic explanation for stone formation (e.g., renal tubular acidosis, hyperparathyroidism, acromegaly, Cushing's syndrome), chronic urosepsis, creatinine ≥1.8 mg/dl (137 μmol/liter), or chronic small or large bowel disease. Study size was established on the basis of the assumption that approximately 40 percent of subjects would have a second stone event during a 3-year period (31, 32) and that the intervention diet would reduce the risk of recurrence by about two thirds ($\alpha = 0.05$, $\beta = 0.20$, two-tailed test). We sought to recruit 54 subjects for each trial group. Informed consent was obtained, and the study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

Baseline information

We collected baseline data on serum calcium, phosphate, creatinine, and uric acid as well as on 24-hour urinary creatinine, calcium, oxalate, urea, and uric acid. Radiography of the abdomen was done if no radiographic film had been obtained in the 6 months before passage of the stone. All subjects were interviewed about diet in the previous 3 months by a research dietician using a standardized food frequency questionnaire. Questionnaire results were compared with 3-day diet records collected simultaneously with the first postintervention evaluation at 6 months' follow-up. The two methods were statistically significantly correlated for nutrient measures of interest: protein, oxalates, purines, and dietary fiber. Correlation coefficients in the intervention group ranged from 0.44 for purines to 0.71 for dietary fiber (mean, 0.63); control group correlation coefficients were lower (mean, 0.49). The initial interview included family history of stone formation, race or ethnicity, education, residence, weight, and height. After informed consent, subjects were randomized from a list of random numbers either to receive instruction on a low protein, high fiber diet, as well as recommendations to maintain a high fluid intake and a controlled calcium intake, or to receive instruction to maintain a high fluid intake and a controlled calcium intake alone. Randomization occurred within 1 year after initial stone event.

Dietary intervention

Persons in the intervention group were instructed to decrease their intake of animal flesh proteins and other purine-containing foods by avoiding a list of nine meats and three legumes and limiting their intake to three 1-ounce servings daily from a list of seven meat and dried legumes groups. Cheeses, eggs, and peanut products were suggested as additional sources of protein. Total protein content of this diet was estimated at 56–64 g daily, and the purine from animal protein and legumes was approximately 75 mg daily. In addition, the intervention subjects were instructed to consume fruits, vegetables, and whole grain products high in fiber, and specifically about one-fourth cup of unprocessed bran daily. Subjects were instructed by a study dietician who described allowable protein intake, sources of fiber, and how to follow this diet.

Both intervention and control subjects were instructed to consume two daily servings of dairy products from a list of 11 options. For persons unwilling or unable to eat dairy products, 500 mg of calcium carbonate were recommended. Finally, both intervention and control subjects were instructed to drink six to

eight glasses of liquid daily, including one at bedtime, to keep the urine dilute.

Follow-up period

Subjects visited the medical center research clinic every 6 months for up to 4 years after randomization and were followed for 4.5 years. At 6 months and at 1.5, 2.5, and 3.5 years, subjects completed a dietary food frequency questionnaire for the previous 3 months and provided blood and 24-hour urine specimens. These specimens were analyzed for the same constituents measured at baseline. In addition, the subjects had an annual abdominal radiograph taken at 1, 2, 3, and 4 years. Abdominal radiographs were done with balloon pressure to minimize obscuration of stones by overlying intestinal contents (33). Although we attempted to get all subjects into the clinic promptly, 6 months was allowed to complete the dietary interview and laboratory studies after a stone event or the end of the formal 4-year follow-up period.

Outcome assessment

Stones that were passed, surgically removed, or radiographically visible were counted as recurrences if they were not present on the baseline radiographs. Renal colic, alone or with hematuria, was not classified as a recurrent stone event. One author (B. E.) assessed each instance of presumed stone formation, passage, or both to determine validity of the event. All available information from the attending physician and the medical records was used, but the referee (B. E.) was kept blind to the intervention or control status of the subject.

Analysis

The statistical significance of the difference in stone formation rate between intervention and control groups was determined from an exact conditional test for equality of incidence rates (34). Differences in mean values of nutrient intake and laboratory values across study groups were compared by using t tests. For each study group, the distribution of time to stone recurrence was estimated by the product limit method (35). The relative risk of stone recurrence was estimated by using Cox proportional hazards models with adjustments made for age as a continuous variable, sex, educational status (beyond high school vs. completion or noncompletion of high school), baseline daily protein intake (5-g increments), and baseline daily fluid intake (100-ml increments).

RESULTS

Study subjects (n = 102) were randomized to intervention and control groups of 51 each. However, three subjects were ineligible and were excluded from the study because stones visible on their radiographs were not recognized at randomization but were seen on a second review of the films. In the intervention group, only 72 percent were men compared with 86 percent in the control group (p = 0.10) (table 1). Mean age was not significantly different between the groups. No significant difference was found in educational status, family history of kidney stones, or body mass index. In both groups, 77 percent of subjects were white, 13 percent were Asian, 5 percent were Hispanic, and 4 percent were black.

Baseline dietary intake was similar for both groups except for total protein, of which the intervention group reported significantly lower consumption (p = 0.02). Both fluid and purine intake was less in the intervention group, although the difference was not statistically significant (table 2). Baseline urine chemistry values also were similar: The mean calcium excretion was almost the same for both intervention and control groups (p = 0.97), and the mean level of urinary uric acid excretion also was similar (p = 0.91) (table 3). The proportion of subjects with hypercalciuria (>300 mg/day (7.5 mmol/day) in men and >250 mg/day (6.2 mmol/day) in women) was not different between intervention and control groups (17.1 vs. 19.4 percent, p = 0.79).

Of the 99 subjects, 21.2 percent were lost to complete follow-up (16.0 percent in the intervention group and 26.5 percent in the control group) because they did not complete the study or (in one case) because an individual moved from the area. A comparison of the 21 subjects who did not complete 4.5 years of follow-up with those 78 who did revealed no significant difference in baseline demographic or dietary intake characteristics except that the dropouts reported lower levels of education (p = 0.01). Furthermore,

TABLE 1. Demographic characteristics of study subjects with a single documented kidney stone, San Francisco, Walnut Creek, and Martinez, California, Kaiser Permanente Medical Care Program, 1983–1985

Variable	Intervention (n = 50)	Control (n = 49)
Men (%)	72.0	85.7
Age (years) (mean ± SE*)	43.1 ± 1.5	42.9 ± 1.4
Education (%)		
High school	20.0	32.7
Partial college	36.0	20.4
College	20.0	30.6
Postgraduate	24.0	16.3
Race (% white)	80.0	73.5
Family history (%)	20.0	19.2
Body mass index (kg/m^2) (mean ± SE)	24.9 ± 0.5	25.8 ± 0.6

* SE, standard error.

TABLE 2. Baseline dietary intake reported by food frequency questionnaire among subjects with a single documented kidney stone, San Francisco, Walnut Creek, and Martinez, California, Kaiser Permanente Medical Care Program, 1983–1985

Variable	Intervention (n = 49)		Control (n = 49)	
	Mean	SE*	Mean	SE
Protein (g)	84.8	4.3	104.4	6.7†
Purine (mg)	304.2	26.3	353.0	28.8
Oxalate (mg)	223.6	20.6	231.4	23.3
Total fiber (g)	24.9	1.5	24.0	1.7
Total fluids (ml)	2,511	146	3,104	338
Water (ml)	1,019	112	1,401	270

* SE, standard error.
† $p = 0.02$.

even though these subjects stopped participating in the trial, 17 of them continued to participate in the health plan, and their records indicated no evidence of recurrent stones in the 4.5-year follow-up period.

Fourteen persons developed stones during a mean follow-up of 3.4 years: two persons in the control group and 12 persons in the intervention group (table 4) (figure 1). The rate of recurrence was 1.2 per 100 person-years in the control group and 7.1 per 100 person-years in the intervention group. This difference was contrary to our hypothesis, statistically significant, and substantial.

Both dietary interviews and laboratory data provided evidence of the expected impact of the intervention. On the basis of reported dietary intake, intervention subjects had notably lower protein intake at the 6-month interview; this difference persisted, although diminished, until the end of follow-up (figure 2). Mean reported purine intake in the intervention group was 62–70 percent of that reported in the control group from the 6 months visit to the last visit at about 3.5 years of follow-up. Total fiber intake was greater in the intervention group, and oxalate intake was similar in both groups. Reported fluid intake (mainly water) was 38 percent greater in the controls at baseline, although it did not increase substantially thereafter.

We found that urinary volume was less for the intervention group at the second (7 percent) and third (15 percent) visit and that urea excretion was less by at least 9 percent in the low protein intervention group throughout the trial, although these differences were not marked (figure 3). Essentially no difference was found in mean calcium excretion between the two groups.

In unadjusted models, the relative risk of stone recurrence was 5.8 (95 percent confidence interval 1.3–26.1) among the intervention group compared with the control group (table 3). Because we were concerned about the possible confounding effects of socioeconomic status (as measured by years of education completed), sex, and baseline protein and fluid intake, we examined the recurrence of stones in proportional hazards models controlling for these factors and found no substantial effect on this risk estimate (relative risk = 5.6, 95 percent confidence interval 1.2–26.1). Finally, we assessed stone recurrence according to compliance with the low protein diet (<70 g daily). Incidence of recurrent stones was greater among the 32 persons who reported a lower mean intake of protein (6.6 vs. 3.0/100 person-years) (p = 0.24).

DISCUSSION

No evidence was found that recommendations to follow a low protein, high fiber diet protected people with single calcium oxalate stones from recurrent kidney stones. In fact, the result contradicted this hypothesis and was highly statistically significant. This unexpected result raised several questions. First, did measures of compliance with the dietary intervention provide evidence that subjects actually followed the diet? Second, was the overall recurrence rate in the intervention group greater than expected, or was the rate among controls lower than expected? In other words, did the dietary intervention actually lead to increased stone formation, or were the controls pro-

TABLE 3. Baseline 24-hour urinary excretion of key determinants of kidney stone formation, San Francisco, Walnut Creek, and Martinez, California, Kaiser Permanente Medical Care Program, 1983–1985

Variable	Intervention		Control	
	Mean ± SE*	No.	Mean ± SE	No.
Volume (ml)	1,510 ± 111	43	1,459 ± 105	37
Creatinine (mmol)	14.3 ± 0.6	41	14.6 ± 0.7	35
Calcium (mmol)	5.21 ± 0.38	42	5.24 ± 0.49	37
Oxalate (mmol)	445 ± 32	41	474 ± 43	35
Urea (mmol)	388 ± 25	37	370 ± 24	27
Uric acid (mmol)	4.36 ± 0.22	43	4.40 ± 0.29	37

* SE, standard error.

TABLE 4. Kidney stone recurrence by intervention status, San Francisco, Walnut Creek, and Martinez, California, Kaiser Permanente Medical Care Program, 1983–1985

Variable	Intervention	Control	*p* value
Subjects	50	49	
Incident stones, no. (%)	12 (24)	2 (4)	
Follow-up (person-years) mean ± SE*	3.4 ± 0.2	3.4 ± 0.2	0.82
Incidence/100 person-years	7.1	1.2	0.006

* SE, standard error.

tected in some way? Third, how can we plausibly explain the observed difference?

We assessed compliance with the dietary intervention through repeated dietary interviews and measurement of urinary chemistry values during the 3.5-year follow-up period. Apart from these contacts, which occurred about every 6 months, we had no other interaction with the subjects. Thus, although the intervention was not as intensive as for a tightly controlled metabolic experiment, a similar frequency and intensity might be expected from motivated interaction of physicians with their patients who had kidney stones. On the basis of notably decreased purine intake (the nutrient most closely linked to animal protein intake) in the intervention group, we concluded that subjects were consuming less animal protein. This was at least partially supported by their lower, although not markedly lower, level of urinary urea. Subjects also reported increased fiber intake, which suggested adherence to the fiber recommendation. However, we believe that the recommendation to consume the fiber supplement was particularly difficult for our subjects to follow because this supplement was unpalatable.

The biomedical literature in English contains little information on expected rate of recurrence among persons who have had a single calcium oxalate stone. In clinical trials published when this trial began in 1983 of persons who had recurrent (two or more) stones, <50 percent of the placebo-treated subjects were free of recurrence after 3 years, giving a mean recurrence rate of approximately 10–15 percent annually (31, 32). We designed our study by expecting about 15 percent of subjects to have a stone recurrence each year.

More recent studies (36–39) have suggested that recurrence rates after a single stone are closer to 7–8 percent. The rate of observed stone recurrence in our trial was consistent with this latter level for the inter-

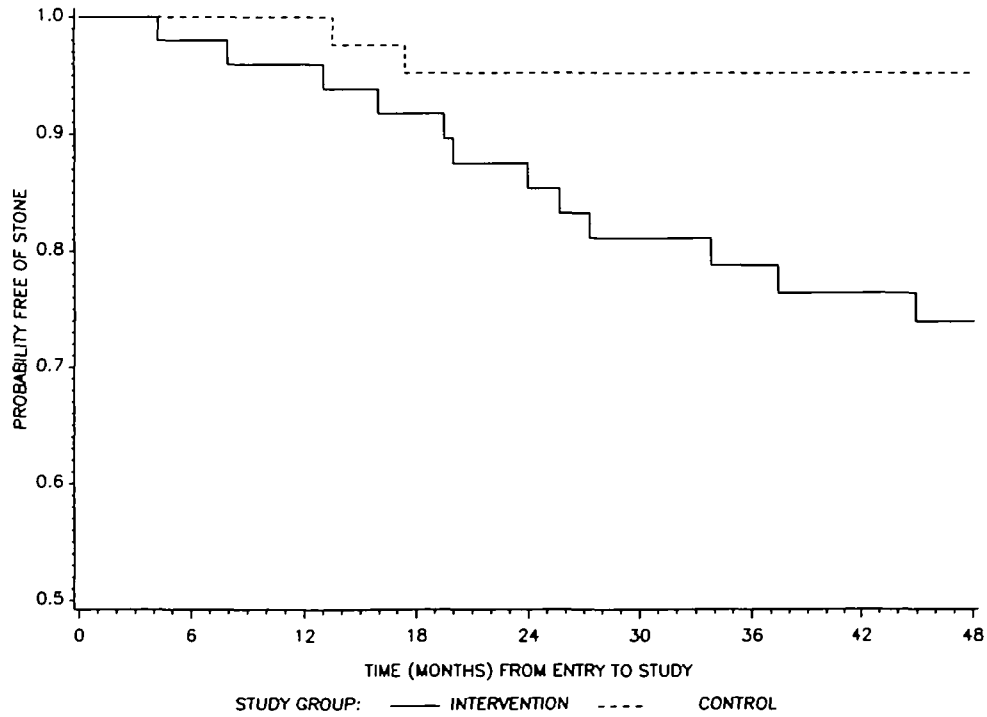

FIGURE 1. Probability of remaining free of kidney stone recurrence by time from date of entry into study among 99 persons who had stones for the first time by study group.

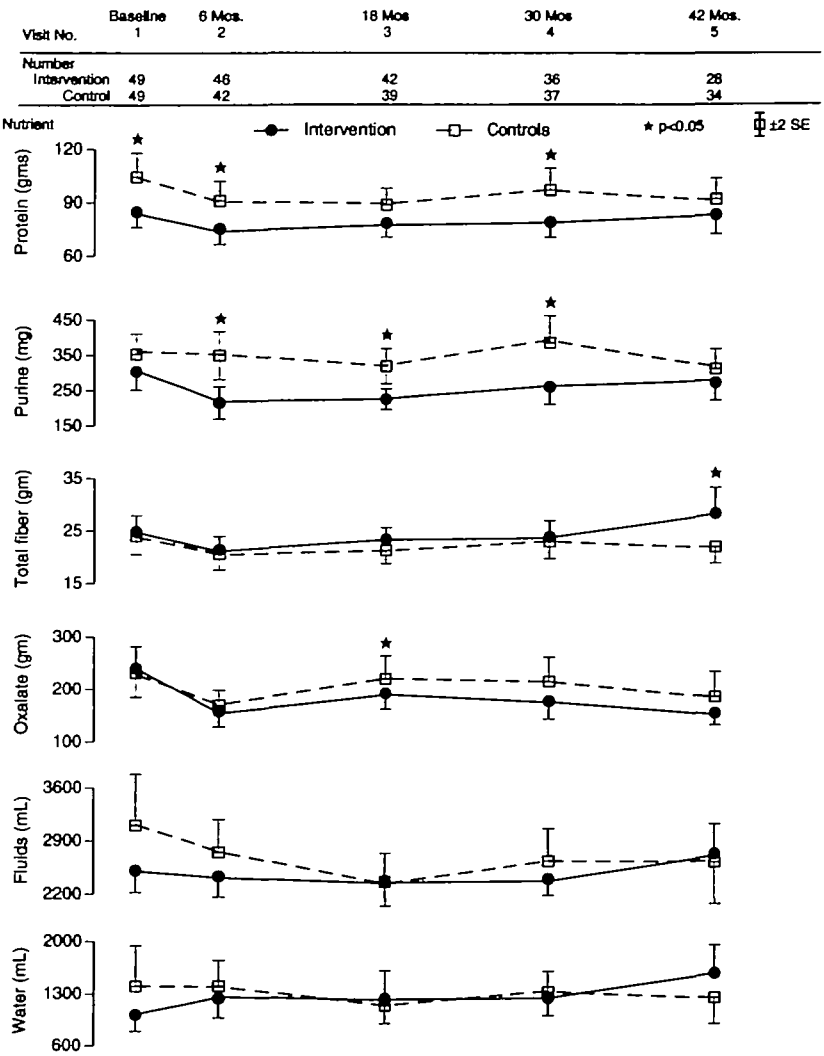

FIGURE 2. Mean (± 2 standard error (SE)) reported nutrient intake from food frequency interviews at baseline (visit 1), 6 months (visit 2), 18 months (visit 3), 30 months (visit 4), and 42 months (visit 5) for intervention and control groups. Time of visit is approximate.

vention group but substantially less than expected in the control group.

We considered possible explanations for the relatively lower recurrence rate among our control subjects. First, increased fluid intake effectively reduces the urinary activity product ratio (saturation) (10) and is one possible explanation. Perhaps the control subjects focused on increasing their fluid intake; however, the intervention subjects, who were following a more complex dietary intervention, might not have followed the fluid recommendations as closely. Reported fluid intake levels were greater among the control subjects in the early part of the trial when most of the stone events occurred (figure 2), although the difference did not persist and measured urinary volumes did not substantially differ in the two groups. Second, the control group could have been constitutionally less likely to form stones; however, levels of calcium and uric acid among intervention and control subjects at baseline were very similar. Likewise, the proportion of subjects with hypercalciuria did not significantly differ in the two groups. Third, characteristics of the intervention may have produced conditions conducive to stone formation. A recent prospective study of physicians by Curhan et al. (11) found a significantly higher incidence of first calcium oxalate stones among men who reported a low dietary calcium intake. In our study, we tried to equalize and not restrict calcium intake but did not measure calcium intake directly in our abbreviated food frequency questionnaire. For calcium intake to explain our observation, our intervention (low protein) group would have had to consume less calcium. We found no evidence for this in the calcium excretion, and the percentage of calcium usu-

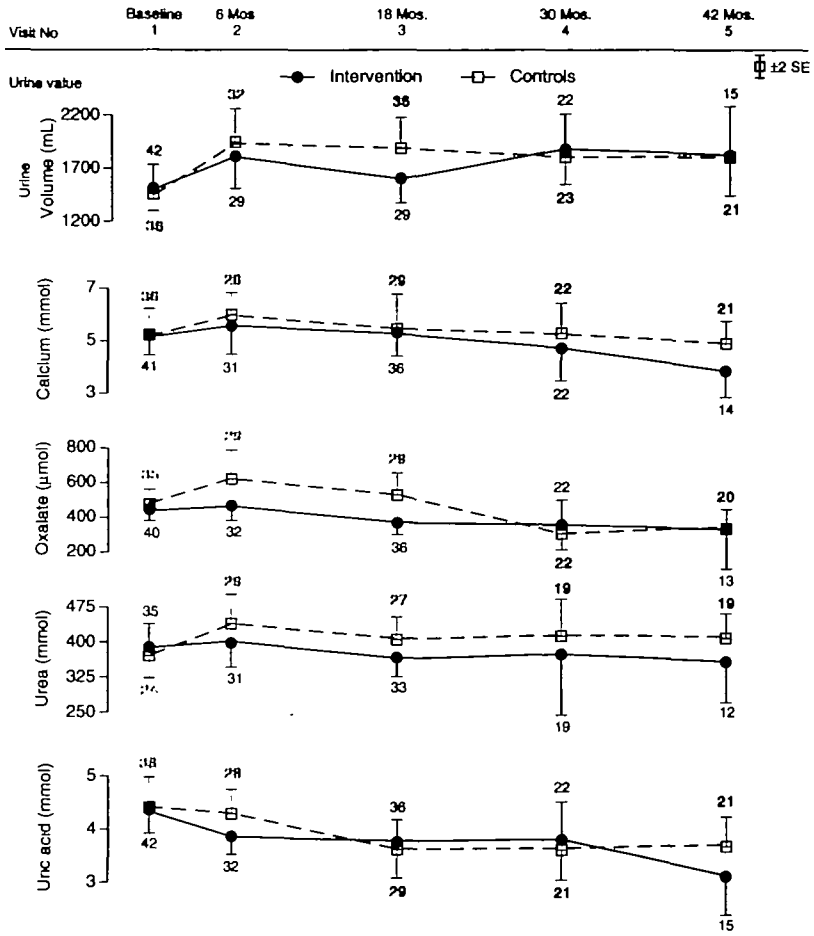

FIGURE 3. Mean (± 2 standard error (SE)) urinary excretion levels at baseline (visit 1), 6 months (visit 2), 18 months (visit 3), 30 months (visit 4), and 42 months (visit 5) for intervention and control groups. Time of visit is approximate.

ally derived from animal protein is small. We believe it unlikely that compliance with a low protein intervention could have contributed to a low calcium intake.

The animal protein hypothesis is well established in the literature (7) and has been advanced by evidence from ecologic correlation research (15) and short-term metabolic studies (16–19), which used small numbers of highly selected subjects. A more recent metabolic study (40) found that animal protein diets can produce urinary changes that increase the risk of uric acid stones but not of calcium oxalate or calcium phosphate stones. Case-control studies (20–22) also noted increased protein intake reported by persons who had stones, but these results were subject to recall bias because dietary information was collected after the stone event. Other case-control studies (23–28) found no difference in animal protein intake. In the only prospective study that addressed this subject (11), results suggested that higher animal protein intake increased the risk of stone formation (p for trend = 0.05), although the greatest risk (relative risk = 1.41, 95 percent confidence interval 1.08–1.85) was found for patients in the middle quintile of animal protein consumption. A recent randomized trial among stone formers found evidence that advice to reduce soft drink consumption resulted in fewer recurrences, but no information was collected on other dietary components (39). The authors suggested that soft drinks may increase the risk of stone formation by the acidifying action of the phosphoric acid they contain (39).

Our study was limited because we could not follow subjects closely to ensure compliance. However, we reasoned that the advice and follow-up we provided were similar to, if not more intensive than, what a physician could provide in the office setting. We were also limited in the number of measurements we could make of dietary nutrients and urinary chemistry values. Therefore, we focused on protein and fiber measurement in the diet instead of on complete ascertainment of nutrients. We did not measure dietary calcium and cannot directly determine its influence on our

results. Finally, we were hampered by missing data because subjects either did not complete the full study or did not provide urine specimens.

We conclude that advice to reduce dietary protein and to increase fiber and fluid intake does not reduce the recurrence rate of calcium oxalate kidney stones compared with simple advice to increase fluid intake. This conclusion conflicts with results from some case-control studies (20–22) and a large prospective study (11), which suggest that high animal protein may increase the risk of a first calcium oxalate stone. Although these were studies of diet as a causal factor in renal stones and not diet as treatment to prevent recurrence, the pathophysiology of first and subsequent stone events should be similar. If confirmed, our results would change current advice given to kidney stone patients. Low protein diets are not harmful and have salutary effects on patients who have cardiovascular diseases or some cancers. However, low protein diets are difficult for physicians to prescribe because they also contain less dietary fat and require most patients to make a major change in eating patterns. The most appropriate advice for the otherwise healthy (and usually young) person who has stones may be to increase water intake instead of attempting to radically modify the diet.

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