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Urinary Lithogenic Risk Profile in Recurrent Stone Formers With Hyperoxaluria: A Randomized Controlled Trial Comparing DASH (Dietary Approaches to Stop Hypertension)-Style and Low-Oxalate Diets

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Background: Patients with nephrolithiasis and hyperoxaluria generally are advised to follow a low-oxalate diet. However, most people do not eat isolated nutrients, but meals consisting of a variety of foods with complex combinations of nutrients. A more rational approach to nephrolithiasis prevention would be to base dietary advice on the cumulative effects of foods and different dietary patterns rather than single nutrients.

Study Design: Randomized controlled trial.

Setting & Participants: Recurrent stone formers with hyperoxaluria (urine oxalate > 40 mg/d).

Intervention: The intervention group was asked to follow a calorie-controlled Dietary Approaches to Stop Hypertension (DASH)-style diet (a diet high in fruit, vegetables, whole grains, and low-fat dairy products and low in saturated fat, total fat, cholesterol, refined grains, sweets, and meat), whereas the control group was prescribed a low-oxalate diet. Study length was 8 weeks.

Outcomes: Primary: change in urinary calcium oxalate supersaturation.

Secondary: Changes in 24-hour urinary composition.

Results: 57 participants were randomly assigned (DASH group, 29; low-oxalate group, 28). 41 participants completed the trial (DASH group, 21; low-oxalate group, 20). As-treated analysis showed a trend for urinary oxalate excretion to increase in the DASH versus the low-oxalate group (point estimate of difference, 9.0 mg/d; 95% CI, −1.1 to 19.1 mg/d; $P = 0.08$). However, there was a trend for calcium oxalate supersaturation to decrease in the DASH versus the low-oxalate group (point estimate of difference, −1.24; 95% CI, −2.80 to 0.32; $P = 0.08$) in association with an increase in magnesium and citrate excretion and urine pH in the DASH versus low-oxalate group.

Limitations: Limited sample size, as-treated analysis, nonsignificant results.

Conclusions: The DASH diet might be an effective alternative to the low-oxalate diet in reducing calcium oxalate supersaturation and should be studied more.

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INDEX WORDS: Dietary Approaches to Stop Hypertension (DASH) diet; oxalate; nephrolithiasis; kidney stone; hyperoxaluria; clinical trial; calcium oxalate supersaturation.

Kidney stone disease is a common, costly, and painful disorder. The lifetime prevalence of symptomatic nephrolithiasis in the United States is ∼10% in men (increasing gradually to a peak of ∼12% in those >70 years) and 5% in women.[1] About 80% of kidney stones contain calcium, and most calcium stones are made up primarily of calcium oxalate.[2] It is likely that dietary changes have contributed in part to the considerable increase in kidney stones in recent decades.[3]

In current clinical practice, the only advice usually given to nephrolithiasis patients with hyperoxaluria[4] is to increase their water intake if consuming a free diet (to reduce urinary oxalate concentration) and to follow a low-oxalate diet (ie, to avoid oxalate-rich foods).[5] Normal dietary calcium intake also has been reported

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to decrease the risk of symptomatic kidney stones.[6,7] However, there are no substantial data supporting the efficacy of the low-oxalate dietary recommendation. Furthermore, a large epidemiologic study showed no significant differences in oxalate intake in people with nephrolithiasis versus non–stone formers.[8]

Interpretation of existing data is complicated because there is inadequate and inaccurate information about the oxalate content of foods, crystalline and soluble forms of oxalate are present in both the diet and during intestinal transit, and the processes involved in intestinal oxalate absorption are incompletely understood. In terms of the latter, in a study by von Unruh et al,[9] gastrointestinal absorption of oxalate in healthy volunteers was reported to be 5%-10%. However, Holmes et al[10] have reported an absorption rate of up to 50%, illustrating the large variation that exists between absorption estimates. Another complicating factor of particular importance is the action of other interfering dietary factors, such as calcium, magnesium,[11] fatty acids, and bile salts.[12] Moreover, colonization with *Oxalobacter formigenes* appears to be associated with less urine oxalate excretion. The restriction of dietary oxalate may reduce not only urine oxalate, but also *O formigenes* colonization because the organism could be deprived of its food source.[13,14] The net effect of these opposing influences is unknown.

Given these complicating factors, a more rational approach to solve the problem of nephrolithiasis might be based on the study of the cumulative effects of foods and different dietary patterns on urinary saturation, rather than on the study of the effect of single nutrients. In other words, clinicians should avoid "restrictive" advice, but rather should encourage the choice of more favorable dietary patterns.

The Dietary Approaches to Stop Hypertension (DASH) diet, which is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein, is the focus of this study. In a previous observational study, people following diets that resembled DASH were found to be less likely to form stones.[15] The basis for this effect was attributable in part to increased urine citrate excretion.[16] A DASH-style diet has higher oxalate and vitamin C content as a result of higher intakes of fruits, vegetables, and nuts, and thus it would be expected to increase urinary oxalate. However, its higher calcium and magnesium content may diminish this effect by lowering the intestinal absorption of oxalate.[16-18] Due to the diet's high amount of fruits and vegetables and low amount of meat products, it also increases urinary citrate excretion, which is an important inhibitor of calcium stones.[16,19]

To our knowledge, no study has been performed on the overall effects of a DASH-style diet on urinary stone risk profile in a randomized clinical trial in recurrent calcium oxalate stone formers. In this study, we compared the effects of a DASH-style diet with an oxalate-restricted diet on urinary lithogenic risk profile and urinary supersaturation in a group of recurrent calcium oxalate stone formers. We hypothesized that a DASH-like dietary pattern would be superior to a low-oxalate diet in lowering urinary calcium oxalate supersaturation.

METHODS

Study Design and Population

This was a randomized controlled trial to compare the effects of a low-oxalate diet with a DASH-style diet. Allocation was concealed. A sample size of 40, with 20 patients in each arm, was calculated to have power to detect a 25% reduction in urinary calcium oxalate supersaturation with 80% sensitivity.

Study participants who were capable of giving informed consent were recruited for the study from the Stone Prevention Clinic of Labbafinejad Hospital in Tehran, Iran. The study was approved by both Urology/Nephrology Research Center and Shahid Labbafinejad Medical Center review boards (approval number 114).

Eligible participants included men and women with a history of at least 2 episodes of calcium oxalate kidney stones (the stone had to be ≥50% calcium oxalate each time) who also had documented hyperoxaluria (urine oxalate > 40 mg/d).[20] Participants who had not had a stone analysis were eligible when their stone was known to be radio-opaque, consistent with calcium composition, and hyperoxaluria was present. Hyperoxaluria had to have been present on both 24-hour urine collections performed before the study when the patients were following their routine diets in the course of their usual evaluation for prescription of a preventive strategy. Patients with urinary abnormalities in addition to hyperoxaluria, including low urine volume, hypercalciuria, hypocitraturia, and hyperuricosuria, were not excluded. Patients were included when they were taking drugs for the prevention of stone disease, including pyridoxine, thiazides (chlorthalidone, hydrochlorothiazide, or indapamide), and allopurinol, as long as there had been no changes in these prescriptions for at least the 3 previous months.

Patients were excluded from participation when they had a history of diabetes, inflammatory bowel disease, ileal or colonic resection, bariatric surgery, chronic kidney disease, or hepatic, thyroid, parathyroid, or immunologic disease. We excluded patients with primary hyperoxaluria or those who were treated with potassium citrate, cholestyramine, or calcium supplements.

When the first set of urine samples confirmed hyperoxaluria, the patients entered the study. A blood sample also was obtained to exclude high parathyroid hormone levels. Information for number of previous kidney stones, hypertension, gout, and family history of kidney stones was obtained. Information for the use of specific medications also was obtained on biennial questionnaires.

After a run-in period of 2 weeks, patients were allocated into 2 groups. The control group was prescribed a low-oxalate diet. They were instructed to avoid very high-oxalate foods entirely and to restrict intake of high-oxalate foods (Table S1, available as online supplementary material). They had no other limitations. The intervention group was asked to follow a calorie-controlled, sodium-restricted DASH diet plan with unrestricted oxalate intake. The DASH plan is an eating pattern recommended by the 2005 US Department of Health and Human Services Dietary Guidelines for Americans as a model of healthy eating for the majority of individuals in the population.[21] This group ate a diet that was higher in fruits, vegetables, and low-fat dairy products and lower in saturated fat, total fat, and cholesterol; it contained more whole grains and fewer refined grains, sweets, and red meat. The

Table 1. Baseline Demographic, Clinical, and Laboratory Values in 41 Recurrent Calcium Oxalate Stone Formers

	All Patients	DASH (n = 21)	Low Oxalate (n = 20)	*P*
Demographic				
Age (y)	48 ± 13	46 ± 15	50 ± 11	0.4
Female sex	31	30	32	0.9
Family history of stones	67	60	74	0.4
Stone recurrence (times)	5 ± 4	6 ± 4	4 ± 3	0.2
Body mass index (kg/m^2)	27.8 ± 4.3	27.3 ± 4.3	28.4 ± 4.4	0.5
Serum measurements				
Fasting plasma glucose (mg/dL)	108.6 ± 24.7	99.9 ± 14.7	117.8 ± 29.8	0.2
Albumin (mg/dL)	4.7 ± 0.5	4.8 ± 0.4	4.6 ± 0.5	0.1
BUN (mg/dL)	14.8 ± 4.7	13.1 ± 4.0	16.5 ± 4.8	0.03
Creatinine (mg/dL)	1.09 ± 0.18	1.04 ± 0.13	1.13 ± 0.22	0.1
Calcium (mg/dL)	9.2 ± 1.5	9.6 ± 0.4	8.8 ± 2.1	0.3
Sodium (mg/dL)	142.9 ± 2.5	142.1 ± 2.2	143.8 ± 2.5	0.05
Potassium (mg/dL)	4.5 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	0.4
Uric acid (mg/dL)	6.7 ± 1.5	6.6 ± 1.3	6.7 ± 1.6	0.7
Phosphorus (mg/dL)	3.1 ± 0.7	3.0 ± 0.7	3.2 ± 0.6	0.3
Alkaline phosphatase (mg/dL)	217 ± 60	219 ± 46	215 ± 74	0.9
24-h urine stone risk profile[a]				
Volume (mL/d)	1,866 ± 564	1,750 ± 482	2,061 ± 622	0.1
Creatinine (g/d)	1.4 ± 0.4	1.4 ± 0.5	1.4 ± 0.4	0.9
Calcium (mg/d)	156.4 ± 64.5	153.8 ± 61.7	164.7 ± 69.9	0.6
Urea (g/d)	22.7 ± 7.2	22.3 ± 7.7	22.6 ± 7.1	0.9
Sodium (mEq/d)	149.5 ± 58.7	152.7 ± 50.6	145.8 ± 71.3	0.7
Potassium (mEq/d)	46.0 ± 15.8	44.6 ± 15.1	47.6 ± 16.7	0.6
Phosphorus (g/d)	0.78 ± 0.33	0.77 ± 0.29	0.79 ± 0.38	0.6
Magnesium (mg/d)	82.9 ± 25.7	73.7 ± 22.3	93.0 ± 26.9	0.02
Chloride (mg/d)	193.1 ± 41.7	197.1 ± 28.5	191.3 ± 53.6	0.7
Uric acid (mg/d)	366.7 ± 131.4	327.1 ± 117.0	408.7 ± 144.0	0.07
Citrate (mg/d)	520.1 ± 345.2	505.7 ± 344.9	571.4 ± 357.5	0.6
Oxalate (mg/d)	50.8 ± 11.4	49.1 ± 8.5	51.1 ± 12.5	0.6
pH	5.72 ± 0.58	5.43 ± 0.35	6.12 ± 0.63	<0.001
Calcium oxalate supersaturation	7.03 ± 3.34	7.16 ± 3.76	6.28 ± 5.38	0.3

Note: As-treated analysis. Values for categorical variables are given as percentages; values for continuous variables, as mean ± standard deviation. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; BUN in mg/dL to mmol/L, ×0.357; glucose in mg/dL to mmol/L, ×0.05551; phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495; uric acid in mg/dL to μmol/L, ×59.48.

Abbreviations: BUN, blood urea nitrogen; DASH, Dietary Approaches to Stop Hypertension.

[a]Mean of the 2 baseline urine collection sample values.

amounts of calcium, potassium, and magnesium in the DASH diet are higher than those in a Western diet. The low-sodium DASH diet contains 2,400 mg of sodium per day. We prescribed adding minimal salt (only1 teaspoon per day) while cooking and insisted on removing table salt. We used the Harris Benedict equation to calculate the energy requirement for each participant.[22] The servings mentioned in the DASH eating plan[21] were used as a practical guideline.

Both groups were advised to drink water in amounts of ~2 L during cold weather and 3 L during warm or hot weather.

The length of the study was 8 weeks. Because this was a dietary intervention, patients were not blinded.

Three-Day Diet Recall

Patients were visited at the beginning of the study, after 4 weeks, and at the end of the study; each session for a patient was 45-60 minutes. There was telephone contact every week with a nutritionist for ongoing reinforcement of the instructions. The nutritionist explained the possible benefits of each diet for patients and told them that if they continued these diets, related metabolic abnormalities might be controlled. An exchange list was given to each patient for exchanging food items and counting the calories. A nutritionist educated participants on how to use the exchange list. Patient adherence to diet was evaluated by a detailed 3-day food recall that was collected from 2 week days and 1 weekend day and was done in 3 nonconsecutive weeks: weeks 1, 4, and 8 (9 recalls total per person). The food recalls were reviewed by a nutritionist when they were submitted and then analyzed using Nutritionist III software, version 7.0 (N-Squared Computing), which was designed for Iranian foods.

Anthropometric Measures

Anthropometric measurements included weight and height and were performed at the beginning of the study, all by the same dietitian. Participants were weighed wearing minimal clothing and without shoes. Height was measured in a standing position, without shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Laboratory Tests

Before study visits, 24-hour urine was collected twice with a 1-week interval, and then at the end of the study, 24-hour urine

was collected once more (last food recall also was completed on the day of last 24-hour urine collection). Mean values of the 2 baseline samples were used as the baseline urine profile data. The 24-hour urine samples were collected in polyethylene containers with hydrochloric acid 6N or boric acid as preservative, stored at −20°C, and analyzed within a month. For metabolic evaluation, urine parameters such as volume, specific gravity, creatinine, phosphate, calcium, oxalate, citrate, sodium, potassium, magnesium, uric acid, pH (in a fresh spot urine sample), urinary supersaturation of calcium oxalate (the main outcome of our study), calcium phosphate, and uric acid were measured using standard methods as follows: sodium (flame photometry; coefficient of variation [CV], 1.9%), potassium (flame photometry; CV, 1.5%), pH (pH meter), specific gravity (refractometry), protein (sulfosalicylic acid assay, quantitative; CV, 2.1%), creatinine (Jaffé kinetic; CV, 1.8%), calcium (Arsenazo, colorimetric; CV, 2.4%), oxalate (enzymatic colorimetric, LTA; CV, 3.57%), uric acid (enzymatic uricase; CV, 4.2%), citrate (enzymatic colorimetric, LTA; CV, 3.18%), magnesium (colorimetric, calmagite; CV, 2.9%), and inorganic phosphate (phosphomolybdate; CV, 2.5%). Urinary supersaturation of calcium oxalate also was calculated at the beginning and end of the study. LithoRisk software (Biohealth) was used to calculate urinary supersaturations.

Statistical Methods

The outcomes of interest were urine lithogenic risk factors, including concentrations of calcium, oxalate, citrate, sodium, potassium, magnesium, and uric acid in 24-hour urine; pH; and especially urinary supersaturation of calcium oxalate (our main outcome). Statistical analyses were performed with the statistical software Stata, version 11.0 (StataCorp LP). Data were presented as mean ± standard deviation. Pearson correlation coefficient (r) was used for analyses of linear associations. Multivariate regression analyses were performed to obtain adjusted P values controlled for covariates. Differences in baseline variables, as well as dietary intakes, between the 2 groups were analyzed using independent-sample t test. A repeated-measure analysis of variance was used to compare 24-hour urinary risk factors between the first and last week of the study period (8 weeks) in both groups. Point estimates for the differences between the 2 groups for changes in urinary lithogenic factors from baseline also were calculated.

RESULTS

Participant Characteristics

Ninety-one individuals were screened for inclusion in the study, 57 of whom had baseline mean urinary oxalate excretion >40 mg/d. Participants were randomly assigned, 29 to a DASH-style diet and 28 to a low-oxalate diet. Four patients randomly assigned to DASH and 2 patients randomly assigned to low-oxalate diets did not follow their assigned diet because their jobs did not allow them to plan for their diets, and so were excluded. Treatment was initiated in 51 patients. Forty-one participants completed the study, 21 in the DASH group and 20 in the low-oxalate group.

Baseline demographic and clinical characteristics and laboratory values of the 41 patients are shown in Table 1. (There were no significant differences in variables in Table 1 between these patients [n = 41] and the original sample [n = 57; data not shown]). Patients' mean age was 48 ± 13 years, mean BMI was 27.8 ± 4.3 kg/m^2, 13 (31%) were women, and 27 (67%) had a family history of stones. Mean recurrence was 5 ± 4 times.

Comparing the DASH and low-oxalate groups, there were no significant differences in age, BMI, family history of stones, or stone recurrence between the 2 groups (Table 1). There were no significant differences between the 2 groups with regard to serum and urine measurements except for serum blood urea nitrogen and sodium and urine magnesium and pH. The 24-hour urine magnesium and pH values tended to be higher in the low-oxalate group ($P < 0.05$ and $P < 0.01$, respectively).

Dietary Intake and Urine Profile

Mean nutrient intakes in the diets of the low-oxalate and DASH groups during the 8-week follow up are shown in Table 2. There were no remarkable differences between the 2 groups with regard to energy,

Table 2. Mean Daily Nutrient Intake in Diets of Both Groups During 8-Week Follow-up

	DASH	Low Oxalate	*P*
Nutrient intake			
Energy (kcal)	1,887 ± 129	1,628 ± 117	0.1
Protein (% of energy)	16.2 ± 0.3	16.1 ± 0.5	0.9
Total fat (% of energy)	24.0 ± 1.1	18.7 ± 1.0	0.002
Saturated fat (% of energy)	6.8 ± 0.4	5.1 ± 0.5	0.006
Polyunsaturated fat (% of energy)	7.0 ± 0.5	5.9 ± 0.4	0.1
Monounsaturated fat (% of energy)	7.2 ± 0.3	4.5 ± 0.3	<0.001
Cholesterol (mg)	191 ± 18	167 ± 25	0.4
Carbohydrate (% of energy)	61.1 ± 1.2	65.9 ± 1.0	0.004
Fiber (g)	15.8 ± 1.3	11.9 ± 0.9	0.03
Calcium (mg)	1,048 ± 78	554 ± 44	<0.001
Oxalate (mg)	195 ± 19	95 ± 15	0.009
Potassium (mg)	2,896 ± 211	1,853 ± 146	<0.001
Magnesium (mg)	278 ± 19	164 ± 13	<0.001
Vitamin C (mg)	173 ± 22	123 ± 18	0.1
Sodium (mg)	2,303 ± 146	2,707 ± 159	0.3
Food groups[a]			
Fruit	3.4 ± 0.4	1.9 ± 0.3	0.008
Vegetables	3.0 ± 0.3	2.1 ± 0.2	0.03
Refined grains	5.5 ± 0.4	7.3 ± 0.8	0.03
Whole grains	4.7 ± 0.7	3.5 ± 0.7	0.3
Low-fat dairy	2.4 ± 0.2	1.1 ± 0.1	<0.001
Regular-fat dairy	0.07 ± 0.06	0.02 ± 0.01	0.4
Nuts, seeds, & legumes	1.5 ± 0.2	0.3 ± 0.0	<0.001
Meats (red, poultry, & fish)	2.1 ± 0.2	3.1 ± 0.4	0.1
Fat & oils	3.6 ± 0.5	3.4 ± 0.5	0.7
Sweets	0.8 ± 0.1	0.7 ± 0.1	0.5

Note: As-treated analysis. Values are given as mean ± standard deviation.

Abbreviation: DASH, Dietary Approaches to Stop Hypertension.

[a]Items in food groups category expressed as servings per day.

Table 3. Urinary Lithogenic Risk Profile of Both Groups at Baseline and End of 8-Week Follow-up

24-h Urine Lithogenic Risk Profile	DASH (n = 21)	Low Oxalate (n = 20)	Point Estimate of Difference (95% CI)	*P* for Difference
Volume			290 (−76 to 655)	0.1
Baseline (mL/d)	1,750 ± 482	2,061 ± 622		
End of trial (mL/d)	2,395 ± 345	2,416 ± 412		
Change (mL/d)	645 (438 to 851)	355 (22 to 688)		
Creatinine			0.23 (0.03 to 0.43)	0.03
Baseline (g/d)	1.41 ± 0.5	1.42 ± 0.4		
End of trial (g/d)	1.42 ± 0.5	1.22 ± 0.4		
Change (g/d)	0.03 (−0.08 to 0.14)	−0.20 (−0.38 to −0.01)		
Calcium			7.2 (−30.7 to 45.3)	0.7
Baseline (mg/d)	153.8 ± 61.7	164.7 ± 69.9		
End of trial (mg/d)	171.6 ± 81.9	175.2 ± 72.4		
Change (mg/d)	17.7 (−9.4 to 44.9)	10.5 (−17.8 to 38.8)		
Urea			5.3 (1.2 to 9.5)	0.02
Baseline (g/d)	22.3 ± 7.7	22.6 ± 7.1		
End of trial (g/d)	26.0 ± 8.5	21.0 ± 8.3		
Change (g/d)	3.7 (0.8 to 6.6)	−1.6 (−4.8 to 1.5)		
Sodium			−19.0 (−52.3 to 14.3)	0.3
Baseline (mEq/d)	152.7 ± 50.6	145.8 ± 71.3		
End of trial (mEq/d)	147.2 ± 73.5	159.3 ± 93.5		
Change (mEq/d)	−5.4 (−24.1 to 13.2)	13.5 (−16.9 to 44.0)		
Potassium			10.5 (−2.5 to 23.6)	0.1
Baseline (mEq/d)	44.6 ± 15.1	47.6 ± 16.7		
End of trial (mEq/d)	56.1 ± 20.1	48.6 ± 22.6		
Change (mEq/d)	11.5 (2.8 to 20.2)	1.0 (−9.6 to 11.5)		
Phosphorus			0.3 (0.1 to 0.5)	<0.001
Baseline (g/d)	0.8 ± 0.3	0.7 ± 0.3		
End of trial (g/d)	0.9 ± 0.4	0.6 ± 0.2		
Change (g/d)	0.2 (0.0 to 0.3)	−0.2 (−0.3 to −0.1)		
Magnesium			17.7 (2.5 to 32.9)	0.03
Baseline (mg/d)	73.7 ± 22.3	93.0 ± 26.9		
End of trial (mg/d)	84.5 ± 31.7	86.1 ± 29.8		
Change (mg/d)	10.8 (−0.03 to 21.6)	−6.9 (−18.3 to 4.5)		
Chloride			−15.7 (−54.5 to 23.0)	0.4
Baseline (mg/d)	197.1 ± 28.5	191.3 ± 53.6		
End of trial (mg/d)	189.5 ± 47.3	199.4 ± 71.7		
Change (mg/d)	−7.5 (−31.9 to 16.8)	8.2 (−24.8 to 41.1)		
Uric acid			67.6 (−31.0 to 188.9)	0.3
Baseline (mg/d)	327.1 ± 117.0	408.7 ± 144.0		
End of trial (mg/d)	338.3 ± 130.0	352.2 ± 130.1		
Change (mg/d)	11.1 (3.1 to 31.1)	−56.4 (−80.1 to 26.1)		
Citrate			221.5 (117.4 to 325.5)	<0.001
Baseline (mg/d)	505.7 ± 344.9	571.4 ± 357.5		
End of trial (mg/d)	625.6 ± 416.2	469.9 ± 267.5		
Change (mg/d)	120.0 (−52.3 to 187.4)	−101.6 (−187.6 to −15.4)		
Oxalate			9.0 (−1.1 to 19.1)	0.08
Baseline (mg/d)	49.1 ± 8.5	51.1 ± 12.5		
End of trial (mg/d)	53.9 ± 14.0	47.0 ± 13.4		
Change (mg/d)	4.8 (−1.8 to 11.4)	−4.2 (−12.4 to 4.0)		
pH			0.6 (0.3 to 0.9)	<0.001
Baseline	5.4 ± 0.3	6.1 ± 0.6		
End of trial	5.9 ± 0.4	6.0 ± 0.7		
Change	0.5 (0.4 to 0.7)	−0.1 (−0.4 to 0.2)		

(Continued)

Table 3 (Cont'd). Urinary Lithogenic Risk Profile of Both Groups at Baseline and End of 8-Week Follow-up

24-h Urine Lithogenic Risk Profile	DASH (n = 21)	Low Oxalate (n = 20)	Point Estimate of Difference (95% CI)	*P* for Difference
Calcium oxalate supersaturation			−1.24 (−2.80 to 0.32)	0.08
Baseline	7.16 ± 3.76	6.28 ± 5.38		
End of trial	4.62 ± 3.11	5.38 ± 2.10		
Change	−2.14 (−3.3 to −0.9)	−0.90 (−1.9 to 0.1)		

Note: As-treated analysis. Values are given as mean ± standard deviation or change value (95% CI).
Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension.

protein, and meat intakes. Percent of calories from total fat and amounts of fiber, calcium, oxalate, potassium, magnesium, fruits, vegetables, whole grain, low-fat dairy, nuts, seeds, and legumes were higher in the DASH group than in the low-oxalate group.

The baseline urinary lithogenic risk profile of study participants and the effects of the 2 diets on 24-hour urinary risk factors and calcium oxalate supersaturation are shown in Table 3. The 24-hour urinary volume increased to a similar extent in both groups. Although oxalate excretion increased mildly and decreased with the DASH and low-oxalate diets, respectively, the difference was not significant. There was a trend for urinary oxalate excretion to increase with the DASH diet versus the low-oxalate diet (point estimate of difference, 9.0 mg/d; 95% confidence interval [CI], −1.1 to 19.1 mg/d; $P = 0.08$), but a trend for calcium oxalate supersaturation to decrease in the DASH versus the low-oxalate group (point estimate of difference, −1.24; 95% CI, −2.80 to 0.32; $P = 0.08$). Magnesium and citrate excretion and urine pH increased in the DASH versus the low-oxalate group (point estimates of difference of 17.7 mg/d [95% CI, 2.5-32.9 mg/d; $P < 0.05$], 221.5 mg/d [95% CI, 117.4-325.5 mg/d; $P < 0.01$], and 0.6 [95% CI, 0.3-0.9; $P < 0.01$], respectively).

Linear Associations

Table S2 shows correlation coefficients for 24-hour urine oxalate concentrations and nutrient intakes in the 41 participants. Oxalate and whole-grain intake were correlated positively with 24-hour urine oxalate excretion ($r = 0.35$ [$P = 0.03$] and $r = 0.54$ [$P < 0.01$], respectively). The correlation between oxalate intake and 24-hour urine oxalate excretion did not persist after multivariate adjustment. The correlation coefficient for whole grain became lower in magnitude after multivariate adjustment, but remained significant. When analyzed within the groups, this correlation was significant in only the DASH group.

Table S3 shows correlation coefficients for 24-hour urine calcium oxalate supersaturation and nutrient intake. Only whole-grain intake was correlated positively with urine calcium oxalate supersaturation ($r = 0.33$; $P < 0.05$). The correlation between oxalate intake and 24-hour urine oxalate excretion did not persist after multivariate adjustment.

Figure S1 shows scatter plots, regression lines, and 95% CIs, reflecting the correlations between whole-grain intake with 24-hour urine oxalate and calcium oxalate urinary supersaturations.

DISCUSSION

To our knowledge, this is the first study comparing the effects of a DASH-style diet with a traditional low-oxalate diet on 24-hour urinary risk factors for stone formation in recurrent stone formers in a randomized clinical trial. In this study, consumption of a DASH-style diet high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein, but with considerable plant protein from legumes and nuts, showed a trend toward an increase in urine oxalate excretion, but a trend toward a decrease in urine calcium oxalate supersaturation.

In 2002, Borghi et al[7] conducted a 5-year randomized trial in recurrent calcium oxalate stone formers with hypercalciuria. They compared 2 diets: one with a "normal" amount of calcium (1,200 mg/d), low animal protein, and reduced sodium intake, and the other was a traditional low-calcium diet. Both groups were instructed to limit oxalate intake. Urinary calcium levels decreased significantly in both groups, but urinary oxalate excretion increased in those following the low-calcium diet while decreasing in those following the normal-calcium, low-animal-protein, low-sodium diet. The effect was attributed to the ability of ingested calcium to bind oxalate in the intestinal lumen and reduce its absorption. In 2 publications, Taylor et al[15,16] evaluated the association of the DASH diet with urinary lithogenic risk factors. In these studies of people following self-selected diets, the authors constructed a DASH score to grade the resemblance of each participant's diet to DASH. They concluded that higher DASH score was associated with higher pH and higher levels of urine potassium, magnesium, and phosphate and lower relative supersaturations of calcium oxalate (in women only) and uric acid and also with reduced risk of nephrolithiasis. However, both these studies were observational.

A possible explanation for our findings of opposite trends on urinary oxalate versus calcium oxalate supersaturation for the DASH versus the low-oxalate diet is the high amount of calcium in the DASH diet, making more calcium available in the intestinal lumen to develop a complex with oxalate, thus decreasing its absorption.[23,24] Also, the reduced intake of protein might decrease the endogenous synthesis of oxalate.[25] However, the potential importance of a reduction in very high-oxalate foods should not be underestimated. However, in terms of supersaturation, the trend toward an increase in oxalate in the DASH group tended to be offset by the increase in urine volume, pH, citrate, magnesium, and potassium (probably due to lower intake of acid load and higher intakes of fruits, vegetables, and nuts). Thus, although in both groups an increase in urinary volume led to a substantial decrease in the calcium oxalate molar product (and thereby of the relative calcium oxalate saturation), urinary supersaturation of calcium oxalate decreased numerically more in the DASH group than in the low-oxalate group.

In our study, we found that urinary calcium increased slightly in both groups; however, this increment was not significant in either of them. The lack of significant increase in urinary calcium excretion, despite high calcium intake in the DASH group, probably is the consequence of decreased sodium intake.[26,27] In addition, the rate of renal net acid excretion is an important determinant of calcium excretion. The greater acid production and net acid excretion (due to more animal protein intake) are accompanied by inhibition of renal tubular calcium reabsorption, which results in a renal calcium leak. Therefore, the lack of significant increase in urinary calcium excretion in the DASH group also can be a consequence of the decreased animal protein intake.[28,29]

An important finding of our study is that whole-grain intake was correlated positively with 24-hour urine oxalate and 24-hour urine calcium oxalate supersaturation in recurrent stone formers. This correlation persisted in the DASH group, but not in the low-oxalate group after multivariate adjustment. Lack of this correlation in the low-oxalate group could be a result of a lower amount of whole grain in this group's diet in comparison to the DASH group's diet. In other words, this correlation may be present with only very high amounts of whole grain. When we looked more closely at the difference in consumption of refined grain and whole grain in the diet of the 2 groups, we found the main reason for less whole-grain intake in those in the low-oxalate group was that they consumed less bran, which is on the list of high-oxalate foods. In general, flours are prepared by milling whole cereal grain into a fine meal, which then is used as an ingredient in various baked goods.[30] In modern milling of whole cereal grains, the kernel goes through a high-heat milling process whereby the germ and bran (which contain 90% of the kernel's nutritional content) are removed, leaving just the endosperm (starch).[30] The starch, when ground finely, results in "refined" flour.[30] In Iran, white rice together with Taftoon and Lavash breads are the source of most refined grains, while whole grains are found in Barbari and Sangak bread. Softer whole grains, including barley, oat, millet, teff, and brown rice, do not normally exist in the markets in Iran as whole grain and so are not prominent in the diets of the patients in this study.

Some limitations should be considered in interpreting our findings. First is the potential for bias because of participants not completing the protocol, requiring an "as-treated" analysis, and limited sample size, which prevents a more detailed analysis of the association of whole grain and urinary lithogenic factors in subgroup analyses. Second, we collected only a single urine specimen at the end of follow-up for the purposes of assessing the lithogenic risk profile. Opinions differ regarding the adequacy of a single collection in the medical evaluation of urolithiasis.[31,32] Third, a main weakness of the study is that dietary calcium was less than desirable in the low-oxalate diet, with a mean intake of 554 mg/d measured by dietary recall. Possible reasons are the potential discrepancies between actual nutrient intake and intake measured by the food recalls. However, these discrepancies would be random concerning case status and therefore could bias our study results toward the null. Fourth, this study population comprised Iranians of Persian ethnicity; therefore, results may not necessarily be generalizable to other ethnic populations.

There are also several strengths to this study, including randomization of our patients, telephone follow-ups, and collections of dietary recalls, the last 2 of which were done regularly and constantly during the treatment period for those who completed the protocol.

We conclude that the DASH diet could represent a novel strategy worthy of study in the prevention of high urinary calcium oxalate supersaturation, in addition to the conventional low-oxalate diet. Changes to the original DASH diet, including combining DASH with restricted oxalate intake, would be expected to boost the effectiveness of the original DASH diet for stone prevention. However, because the DASH diet includes high amounts of whole grain (such as rice bran) and we saw a linear correlation between this dietary factor and urinary oxalate and calcium oxalate supersaturation, very high amounts of whole grain (>6-7 servings), especially bran, should be avoided. Future randomized

controlled studies with various amounts and kinds of whole grain are needed in order to obtain clearer conclusions.

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SUPPLEMENTARY MATERIAL

Table S1: Foods considered very high or high in oxalate.

Table S2: Correlation coefficients for 24-hour urine oxalate and nutrient intakes.

Table S3: Correlation coefficients for urine calcium oxalate supersaturation and nutrient intakes.

Figure S1: Correlations between whole grain intake with 24-hour urine oxalate and calcium oxalate urinary supersaturation.

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