Determinants of 24-hour Urinary Oxalate Excretion

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Background and objectives: Higher levels of urinary oxalate substantially increase the risk of calcium oxalate kidney stones. However, the determinants of urinary oxalate excretion are unclear. The objective was to examine the impact of dietary factors, age, body size, diabetes, and urinary factors on 24-h urinary oxalate.

Design, setting, participants, and measurements: We conducted a cross-sectional study of 3348 stone forming and non–stone-forming participants in the Health Professionals Follow-up Study (men), the Nurses' Health Study (older women), and the Nurses' Health Study II (younger women).

Results: Median urinary oxalate was 39 mg/d in men, 27 mg/d in older women, and 26 mg/d in younger women. Participants in the highest quartile of dietary oxalate excreted 1.7 mg/d more urinary oxalate than participants in the lowest quartile (P trend 0.001). The relation between dietary and urinary oxalate was similar in individuals with and without nephrolithiasis. Participants consuming 1000 mg/d or more of vitamin C excreted 6.8 mg/d more urinary oxalate than participants consuming <90 mg/d (P trend < 0.001). Body mass index, total fructose intake, and 24-h urinary potassium, magnesium, and phosphorus levels also were positively associated with urinary oxalate. Calcium intake and age were inversely associated with urinary oxalate. After adjustment for body size, participants with diabetes excreted 2.0 mg/d more urinary oxalate than those without diabetes (P < 0.01).

Conclusions: The impact of dietary oxalate on urinary oxalate appears to be small. Further investigation of factors influencing urinary oxalate may lead to new approaches to prevent calcium kidney stones.

Clin J Am Soc Nephrol 3: 1453–1460, 2008. doi: 10.2215/CJN.01410308

Approximately 80% of kidney stones contain calcium, and the majority of calcium stones consist primarily of calcium oxalate (1). Small increases in urinary oxalate have a major effect on calcium oxalate crystal formation (2), and higher levels of urinary oxalate substantially increase the risk for calcium oxalate kidney stones (3). Despite the importance of urinary oxalate in the pathogenesis of calcium nephrolithiasis, the determinants of urinary oxalate excretion are unclear.

Because oxalate is a metabolic end-product and is excreted unchanged in the urine after absorption in the gastrointestinal tract, clinicians routinely recommend a low oxalate diet to patients with calcium oxalate nephrolithiasis (4). However, the effect of dietary oxalate on urinary oxalate is controversial. A large amount of urinary oxalate is derived from the endogenous metabolism of glycine, glycolate, hydroxyproline, and vitamin C (5,6), and estimates of the proportion of urinary oxalate derived from dietary oxalate vary widely (from 10% to 50%) (7). It is also uncertain whether stone formers have higher levels of intestinal oxalate absorption than non-stone formers (8,9).

Additional factors (including body size and the intakes of calcium, magnesium, vitamin C, and vitamin B6) may influence urinary oxalate excretion by modulating endogenous oxalate production (5,6) or intestinal oxalate absorption (10), but the importance of these factors is also unclear. The results of many feeding studies may have limited applicability to free-living populations. For example, although 1000 mg of supplemental vitamin C consumed twice daily increases urinary oxalate excretion by 22% (11), the effect of lower, more commonly consumed doses of vitamin C on urinary oxalate excretion is uncertain. Previous population-based studies have been relatively small and provide conflicting results about the associations between vitamin C intake, body size, and urinary oxalate (12,13). No population-based study to date has examined the relations between urinary oxalate and the intake of individual amino acids (such as tryptophan, serine, and glycine) or specific carbohydrates (such as fructose) that may be important for oxalate synthesis (14). Finally, the impact of age and diabetes on urinary oxalate excretion is unknown.

To examine the relations between specific demographic, dietary, and urinary factors and the 24-h urinary excretion of oxalate, and to determine whether these associations varied by kidney stone history, we conducted a cross-sectional study of 3348 individuals with and without a history of kidney stones from three cohorts: the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Studies I and II (NHS I and NHS II).

Received March 24, 2008. Accepted June 16, 2008.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/305–1453

Materials and Methods

Source Population

HPFS. In 1986, 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians between the ages of 40 and 75 yr enrolled in HPFS by completing and returning an initial questionnaire that provided detailed information on medical history, lifestyle, and medications.

NHS I. In 1976, 121,700 female registered nurses between the ages of 30 and 55 yr enrolled in NHS I by completing and returning an initial questionnaire.

NHS II. In 1989, 116,671 female registered nurses between the age of 25 and 42 yr enrolled in NHS II by completing and returning an initial questionnaire.

HPFS, NHS I, and NHS II have been followed by biennial mailed questionnaires that ask about lifestyle practices and other exposures of interest, as well as newly diagnosed diseases. The follow-up for all three cohorts exceeds 90%.

Ascertainment of Diet

A semiquantitative food-frequency questionnaire (FFQ) asking about the average use of more than 130 foods and beverages during the previous year has been mailed to study participants every 4 yr. Intake of specific dietary factors was computed from the reported frequency of consumption of each specified unit of food and, with the exception of oxalate, from U.S. Department of Agriculture data on the content of the relevant nutrient in specified portions. The oxalate content of the majority of foods was measured by capillary electrophoresis in the laboratory of Dr. Ross Holmes (methods described in detail elsewhere (15,16)). Nutrient values were adjusted for total caloric intake to determine the nutrient composition of the diet independent of the total amount of food eaten (17,18). The intake of supplements (such as calcium and vitamin C) in multivitamins or isolated form was determined by the brand, type, and frequency of reported use.

The reproducibility and validity of the FFQs were documented previously (19,20).

Ascertainment of Other Covariates

Information on age, weight, and height was obtained on the baseline questionnaire. Self-reported weight was updated every 2 yr. Self-reported weight has been validated in HPFS and NHS I (21). Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Information on hypertension, diabetes mellitus, and kidney stones was obtained from biennial questionnaires. The validity of these self-reported diseases has been documented (16,22–24). Information on family history of kidney stones was obtained in 1994 in HPFS and in 1997 in NHS II.

Urine Collections and Exclusion Criteria

Twenty-four-hour urine samples were collected in two cycles as part of a study to compare the urine composition of stone formers to non-stone formers. In the first cycle, which spanned from 1994 to 1999, we obtained one 24-h urine collection from 1046 participants (25). The second cycle began in 2003 when we invited additional stone formers and randomly selected controls to perform two 24-h urine collections. In the first cycle, participants were ineligible if they were more than 70 yr of age in HPFS or more than 65 yr in NHS I or had a history of cancer or cardiovascular disease. In the second cycle, participants were ineligible if they were older than 75 yr or had a history of cancer (other than nonmelanoma skin cancer).

The rates of participation and completion among stone-forming and non–stone-forming participants in each cohort were reported previously (3). The 24-h urine collection procedure used in this study was performed using the system provided by Mission Pharmacal (San Antonio, TX), and has been described in detail elsewhere (3). The demographic characteristics and dietary intake of participants who collected urine and those who did not were similar (3).

In the present study, we excluded participants with missing information on diet or BMI, participants who reported a history of ulcerative colitis or Crohn's disease, and participants with 24-h urinary creatinine values in the top 1% or bottom 1% of the urinary creatinine distribution of non-stone formers in each cohort. After exclusions, 1032 HPFS participants, 1239 NHS I participants, and 1077 NHS II participants provided at least one 24-h urine collection, and a total of 2278 participants completed two collections.

Analytic Procedures Used for the Urine Measurements

Calcium and magnesium were measured by an atomic absorption spectrophotometer. Creatinine, uric acid, citrate, and phosphorus were measured by a Cobas centrifugal analyzer. Oxalate was analyzed by ion chromatography. Sodium and potassium were determined directly by flame emission photometry. We previously sent blinded split samples to assess reproducibility; the coefficients of variation for all factors analyzed were less than 10%.

Statistical Analysis

In the primary analysis, we included participants who provided a single 24-h urine collection. If a participant submitted more than one 24-h urine collection, we used the first sample. In secondary analyses, we studied participants who submitted two collections. Participants were included only if the creatinine value in each urine collection differed by less than 30% from the mean creatinine value of the two collections. Values for urinary oxalate (and other urinary factors) were obtained by calculating the arithmetic mean of both collections.

To examine the independent relations between demographic, dietary, and urinary factors and the 24-h urinary excretion of oxalate, we constructed multivariate linear regression models with 24-h urinary oxalate as the dependent variable. Independent variables considered in the multivariate analyses were age (continuous), BMI (continuous), history of hypertension (yes or no), history of diabetes (yes or no), history of kidney stones (yes or no), family history of kidney stones (yes or no), cohort (HPFS, NHS I, or NHS II), dietary intakes of oxalate, calcium, total animal protein, total fructose, serine, glycine, and tryptophan (all in quartiles), total intakes of vitamin C (five categories) and vitamin B6 (quartiles), supplemental calcium use (four categories), and urinary factors, including total volume, pH, and the 24-h urinary excretion of calcium, citrate, uric acid, sodium, magnesium, potassium, phosphate, and creatinine (all in quartiles). Cohort-specific quartiles were determined before study participants were merged into a single data set.

All P values are two-tailed. We calculated 95% confidence intervals for all estimates. Data were analyzed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC). The research protocol for this study was approved by the institutional review board of Brigham and Women's Hospital.

Results

Characteristics of men (HPFS), older women (NHS I), and younger women (NHS II) who provided a 24-h urine collection are displayed in Table 1. The majority (>60%) of participants had a history of kidney stones. Dietary oxalate and total vitamin C intakes were higher in men than women, as was the urinary excretion of potassium, magnesium, phosphate, and

Table 1. Characteristics of study participants by cohort

	HPFS (n = 1032)	NHS I (n = 1239)	NHS II (n = 1077)
Age (yr)	63.4 (58.8–69.3)	66.2 (61.3–71.5)	49.6 (45.1–53.8)
BMI (kg/m^2)	25.8 (23.7–28.0)	26.0 (22.9–29.8)	25.4 (22.5–30.7)
History of kidney stones (%)	62.7	69.1	62.9
History of hypertension (%)	35.6	49.0	22.2
History of diabetes (%)	5.8	9.8	4.5
Family history of kidney stones (%)	18.0	NA	25.3
Dietary oxalate (mg/d)	190 (141–246)	156 (116–201)	160 (117–218)
Dietary calcium (mg/d)	769 (627–976)	733 (572–950)	824 (661–1071)
Supplemental calcium (mg/d)	0 (0–200)	401 (0–950)	200 (0–700)
Total vitamin C intake (mg/d)	239 (148–614)	203 (135–477)	165 (108–276)
Urinary potassium (mEq/d)	73 (58–91)	58 (45–72)	52 (41–66)
Urinary magnesium (mg/d)	118 (94–147)	95 (74–122)	94 (74–121)
Urinary phosphate (mg/d)	1033 (852–1249)	729 (591–897)	807 (649–999)
Urinary sodium (mEq/d)	173 (134–224)	132 (99–172)	144 (109–182)
Urinary creatinine (mg/d)	1633 (1384–1900)	1029 (881–1185)	1168 (1016–1359)
Urinary oxalate (mg/d)	39 (31–47)	27 (22–33)	26 (21–32)

Data are presented as median (25th to 75th percentile) unless otherwise indicated. HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; BMI, body mass index; NA, not applicable.

creatinine. Men consumed less supplemental calcium than women and excreted more urinary oxalate.

Because the relations between each demographic, dietary, and urinary factor and urinary oxalate were similar in each cohort and also were similar in stone formers and non-stone formers (with the exception of dietary calcium), we combined all participants. Age was independently and inversely associated with urinary oxalate (Table 2). After multivariate adjustment, every 5-yr increase in age was associated with a 0.6 mg/d ($P < 0.001$) decrease in urinary oxalate. Larger body size was positively associated with 24-h urinary oxalate excretion (Table 2). After multivariate adjustment, a 1-kg/m^2 increase in BMI was associated with a 0.3-mg/d ($P < 0.001$) increase in urinary oxalate and every 5-kg increase in weight was associated with a 0.6-mg/d ($P < 0.001$) increase in urinary oxalate. After multivariate adjustment (which included adjustment for weight), participants with a history of diabetes excreted 2.0 mg/d ($P = 0.004$) more urinary oxalate than their nondiabetic counterparts (Table 2). Hypertension was not associated with urinary oxalate.

Table 2. Multivariate-adjusted differences in 24-h urinary oxalate excretion by age, BMI, weight, and history of diabetes

	Difference in Urinary Oxalate (mg/d)	95% CI
Age (per 5 yr increment)[a]	−0.6	−0.9 to −0.4
BMI (per kg/m^2)[b]	0.3	0.2 to 0.4
Weight (per 5-kg increment)[c]	0.6	0.5 to 0.7
History of diabetes[d]	2.0	0.7 to 3.3

[a]Adjusted for kidney stone history, cohort, history of diabetes (yes or no), weight (continuous), 24-h urinary excretion of creatinine, potassium, magnesium, and phosphorus (all in quartiles), dietary oxalate and calcium (quartiles), total intake of vitamin C (five categories), and supplemental calcium intake (four categories).

[b]Adjusted as above, except 24-h urinary creatinine and weight not in the model.

[c]Adjusted as above, except 24-h urinary creatinine and BMI not in the model.

[d]Participants without diabetes are the referent group. Adjusted for age, kidney stone history, cohort, weight (continuous), 24-h urinary excretion of creatinine, potassium, magnesium, and phosphorus (all in quartiles), dietary oxalate and calcium (quartiles), total intake of vitamin C (five categories), and supplemental calcium intake (four categories).

Multivariate-adjusted differences in 24-h urinary oxalate excretion by specific dietary and urinary factors are displayed in Table 3. Participants in the highest quartile of dietary oxalate excreted 1.7 mg/d (P trend = 0.001) more urinary oxalate than participants in the lowest quartile of dietary oxalate. Participants consuming 1000 mg/d or more of vitamin C excreted 6.8 mg/d (P trend < 0.001) more urinary oxalate than participants consuming less than the recommended dietary allowance of vitamin C (<90 mg/d). Dietary calcium and supplemental calcium intake were inversely associated with urinary oxalate. Participants in the highest quartile of dietary calcium excreted 2.3 mg/d (P trend < 0.001) less urinary oxalate than participants in the lowest quartile. Participants consuming more than 500 mg/d of supplemental calcium excreted 1.7 mg/d (P trend < 0.001) less urinary oxalate than participants consuming no supplemental calcium. Higher urinary levels of calcium also were associated with lower urinary oxalate. After adjusting for 24-h urinary creatinine, participants in the highest quartile of urinary calcium excreted 1.9 mg/d (P trend < 0.001) less uri-

Table 3. Multivariate-adjusted differences in 24-h urinary oxalate excretion by category of dietary or urinary factor[a]

	Difference in Urinary Oxalate (mg/d)	95% CI	*P* for Trend
Dietary oxalate			
quartile 1	Referent		
quartile 2	1.2	(0.3 to 2.1)	
quartile 3	1.3	(0.4 to 2.2)	
quartile 4	1.7	(0.8 to 2.6)	
			0.001
Dietary calcium			
quartile 1	Referent		
quartile 2	−1.4	(−2.4 to −0.5)	
quartile 3	−2.1	(−3.0 to −1.2)	
quartile 4	−2.3	(−3.2 to −1.3)	
			<0.001
Supplemental calcium			
None	Referent		
1 to 100 mg/d	−0.3	(−1.6 to 1.1)	
101 to 500 mg/d	−1.0	(−1.8 to −0.1)	
>500 mg/d	−1.7	(−2.7 to −0.8)	
			<0.001
Total vitamin C			
<90 mg/d	Referent		
90 to 249 mg/d	2.1	(1.0 to 3.2)	
250 to 499 mg/d	3.5	(2.2 to 4.9)	
500 to 999 mg/d	3.6	(2.2 to 5.0)	
≥1000 mg/d	6.8	(5.2 to 8.3)	
			<0.001
Urinary potassium			
quartile 1	Referent		
quartile 2	1.3	(0.3 to 2.2)	
quartile 3	2.6	(1.6 to 3.6)	
quartile 4	4.3	(3.2 to 5.4)	
			<0.001
Urinary magnesium			
quartile 1	Referent		
quartile 2	0.7	(−0.2 to 1.6)	
quartile 3	1.5	(0.5 to 2.4)	
quartile 4	3.4	(2.4 to 4.4)	
			<0.001
Urinary phosphorus			
quartile 1	Referent		
quartile 2	2.1	(1.1 to 3.0)	
quartile 3	1.7	(0.7 to 2.7)	
quartile 4	3.6	(2.5 to 4.8)	
Urinary creatinine			<0.001
quartile 1	Referent		
quartile 2	1.2	(0.2 to 2.2)	
quartile 3	2.3	(1.3 to 3.4)	
quartile 4	3.8	(2.6 to 5.0)	
			<0.001

[a]Adjusted for age, kidney stone history, cohort, weight (continuous), 24-h urinary excretion of creatinine, potassium, magnesium, and phosphorus (all in quartiles), dietary oxalate and calcium (quartiles), total intake of vitamin C (five categories), and supplemental calcium intake (four categories).

nary oxalate than those in the lowest quartile. Higher urinary levels of potassium, magnesium, and phosphorus all were independently associated with higher urinary oxalate. Compared with participants in the lowest quartile of each urinary factor, the multivariate-adjusted increases in urinary oxalate for those in the highest quartile were 4.3 mg/d (P trend < 0.001) for urinary potassium, 3.4 mg/d (P trend < 0.001) for urinary magnesium, and 3.6 mg/d (P trend < 0.001) for urinary phosphorus. Participants in the highest quartile of urinary creatinine excreted 3.8 mg/d (P trend < 0.001) more urinary oxalate than participants in the lowest quartile.

The magnitude of the inverse relation between dietary calcium and urinary oxalate excretion was greater in participants with a history of kidney stones than in participants without a history of kidney stones (Table 4; P for interaction < 0.001). The associations between other factors (including dietary oxalate) and the excretion of urinary oxalate did not vary by stone-forming status.

The intakes of total animal protein, vitamin B6, glycine, tryptophan, and serine were not associated with urinary oxalate. Urinary factors not associated with urinary oxalate included total volume, pH, citrate, uric acid, and sodium. Neither a family history of kidney stones nor the use of thiazide diuretics was associated with urinary oxalate.

We also studied participants who submitted two 24-h urine collections. For 24-h urinary oxalate, the average within-pair coefficients of variation (comparing the first to the second urine collection) were 17% in men, 15% in older women, and 16% in younger women. Among participants with two urine collections, we observed similar relations with urinary oxalate with the exception of total fructose intake. After multivariate adjustment, individuals in the highest quartile of total fructose intake excreted 1.5 mg/d (95% confidence interval, 0.6 to 2.5; P for trend = 0.004) more urinary oxalate than participants in the lowest quartile. Nonfructose carbohydrates were not associated with urinary oxalate.

Discussion

The results of our study underscore the complexity of urinary oxalate. Nondietary factors, such as body size, age, and diabetes, play a role in urinary oxalate excretion. Consistent with the results of previous population-based studies (12), we observed a relation between larger body size and higher urinary oxalate. Weight, BMI, and urinary creatinine all were positively and independently associated with urinary oxalate. Although the reasons for these associations are unclear, it is likely that body mass increases endogenous oxalate production. We also observed higher levels of urinary oxalate in younger individuals and in individuals with diabetes, even after adjusting for diet and body size. We are unaware of previous studies that specifically examined the impact of age or diabetes on urinary oxalate, and it is unknown whether hepatic oxalate production is altered in states of relative insulin resistance. However, it is interesting to speculate that these observations may account, at least partially, for the lower rate of incident stone disease previously reported in older individuals and the higher rate of stone disease reported in those with diabetes (26,27).

We found only a small association between oxalate intake and levels of urinary oxalate. It is difficult to compare the results of our population-based study with previously published oxalate loading trials because data from many such studies are conflicting. Estimates of the proportion of urinary oxalate derived from dietary oxalate vary widely (generally between 10% and 50% (7)). In addition, some loading studies suggest that absorption of oxalate is much higher at low intakes (7), whereas others describe a constant relationship (28) or report higher absorption with higher oxalate intake (29). Part of

Table 4. Multivariate-adjusted differences in 24-h urinary oxalate excretion by category of dietary calcium, stratified by kidney stone history[a]

Dietary calcium	Difference in Urinary Oxalate (mg/d)	95% CI	P for Trend[b]
Non-stone formers (n = 1168)			
quartile 1	Referent		
quartile 2	−0.4	(−2.0 to 1.2)	
quartile 3	−1.0	(−2.6 to 0.7)	
quartile 4	−0.9	(−2.5 to 0.6)	
			0.21
Stone formers (n = 2180)			
quartile 1	Referent		
quartile 2	−1.9	(−3.1 to −0.8)	
quartile 3	−2.6	(−3.8 to −1.4)	
quartile 4	−3.0	(−4.2 to −1.8)	
			<0.001

[a]Adjusted for age, kidney stone history, cohort, weight (continuous), 24-h urinary excretion of creatinine, potassium, magnesium, and phosphorus (all in quartiles), dietary oxalate (quartiles), supplemental calcium intake (four categories), and total intake of vitamin C (five categories).

[b]P = 0.0005 for interaction between dietary calcium and kidney stone history.

the problem may lie in the assay used in many oxalate loading studies: large intraindividual variability, ranging from 1.7% to 20%, has been reported in normal individuals undergoing ^{13}C-oxalate absorption testing (30). Furthermore, it is unclear if the sodium oxalate preparation used in oral loading studies has similar bioavailability to oxalate found in food.

The small magnitude of the association between dietary and urinary oxalate in our study may reflect the primacy of endogenous oxalate synthesis in determining urinary oxalate levels and is consistent with the modest or null associations between dietary oxalate and kidney stone formation we observed in these cohorts (16). The two largest population-based studies to date examining urinary oxalate excretion (one consisting of 94 healthy adults (12) and the other consisting of 186 calcium oxalate stone formers (13)) found no statistically significant relation between dietary and urinary oxalate; it is possible our results are a reflection of our study's larger population and concomitant increase in statistical power. Our data also suggest that the relation between dietary oxalate and urinary oxalate, at least at levels consumed in the free-living population, is relatively linear. Finally, the relation between dietary oxalate and urinary oxalate was similar in participants with and without stone disease, a finding that does not support the hypothesis that stone formers absorb more intestinal oxalate, on average, than their non–stone-forming counterparts.

The intakes of dietary and supplemental calcium were inversely associated with urinary oxalate, and total vitamin C intake and urinary phosphorus excretion were positively associated with urinary oxalate. Both calcium loading studies and population-based studies previously described the inverse association between calcium intake and urinary oxalate (12,13,31), which presumably is due to binding of intestinal oxalate. The reason for the greater impact of dietary calcium on urinary oxalate in the stone-forming participants of our study is unknown. Previously, a randomized cross-over trial demonstrated that 1000 mg of supplemental vitamin C consumed twice daily increased urinary oxalate excretion by 22% (11). Our data suggest that significant increases in urinary oxalate excretion also occur after consuming much lower doses of vitamin C and that vitamin C intake is an important determinant of urinary oxalate excretion in free-living individuals. Higher vitamin C intake also is associated with an increased risk of kidney stone formation. A prospective study in HPFS found that the multivariate relative risk of kidney stone formation for men consuming 1000 mg or greater of vitamin C per day was 41% higher than those consuming less than the recommended dietary allowance of 90 mg/d (26). To the extent that urinary phosphorus reflects dietary intake, our study suggests that dietary phosphorus is positively associated with urinary oxalate. It is possible that dietary phosphorus binds intestinal calcium, thereby increasing the absorption of dietary oxalate.

We detected a positive relation between total fructose intake and urinary oxalate only after studying participants who provided two urine collections, suggesting that high within-person variability in short-term fructose intake attenuated the association. Although a specific biochemical pathway whereby fructose is metabolized to oxalate has not been identified, it is possible such a pathway exists (14,32–34). Of note, we recently reported a positive relation between fructose intake and the risk of incident kidney stone formation (35).

Higher levels of urinary potassium and magnesium reflect higher potassium and magnesium intake, respectively, but it is unclear why the ingestion of either cation would lead to higher levels of urinary oxalate. It is possible that potassium and magnesium increase oxalate synthesis or absorption via unknown mechanisms. Another possibility is that total food oxalate, which our study measured, is poorly correlated with bioavailable food oxalate. In such a scenario, urinary potassium and magnesium may serve as markers for the intake of bioavailable oxalate in many fruits and vegetables. Individuals who restrict their intake of fruits and vegetables have reductions in urinary oxalate, potassium, and magnesium (36). Unfortunately, there is no accepted assay (beyond measuring increases in urinary oxalate after food ingestion) to determine the oxalate bioavailability of individual foods.

We did not observe an association between animal protein intake and urinary oxalate, nor did we observe associations between the intake of specific amino acids (such as glycine, tryptophan, and serine) and urinary oxalate. There is strong evidence from loading studies that hydroxyproline results in increased urinary oxalate (37). However, we did not have information on hydroxyproline intake.

The limitations of our study deserve mention. First, we studied determinants of 24-h urinary oxalate excretion. Therefore, we could not identify factors influencing postprandial spikes in urinary oxalate, which may be important for kidney stone formation (38). Second, we ascertained long-term dietary patterns with the FFQ, whereas 24-h urine composition is likely to reflect short-term dietary intake. Thus, it is possible that some relations we observed in our study between specific dietary exposures and 24-h urinary oxalate excretion are of greater magnitude than we describe. However, we used urinary factors (such as urinary sodium and potassium) to estimate dietary intake when possible. We also studied participants with two 24-h urine collections to minimize the effect of short-term dietary variation. Third, the environmental factors identified in our study accounted for a minority of variation in urinary oxalate, perhaps suggesting the importance of genetic factors. We currently do not have data on the impact of genetic factors, or gene-environment interactions, on urinary oxalate. Fourth, although we excluded participants with inflammatory bowel disease, we did not have data on other conditions associated with enteric hyperoxaluria. Finally, the generalizability of our results may be limited. We do not have urine collections from younger men, and our study did not include urine collections from nonwhite participants.

Conclusion

Both nondietary and dietary factors are important determinants of 24-h urinary oxalate excretion. Our study confirms the positive relation between body size and urinary oxalate excretion and identifies previously unappreciated independent associations for age and diabetes. Although dietary factors, including vitamin C, play an important role in urinary oxalate

excretion, the impact of dietary oxalate on urinary oxalate appears to be small. Our data do not support the contention that individuals with kidney stone disease, on average, absorb more intestinal oxalate than non-stone formers. Based on the available evidence, we recommend that individuals with calcium oxalate stone disease and higher levels of urinary oxalate discontinue vitamin C supplementation. For many stone formers, restricting dietary oxalate may be a relatively ineffective intervention to reduce urinary oxalate excretion. We hope our study encourages additional research to elucidate factors influencing oxalate bioavailability, intestinal oxalate absorption, endogenous oxalate production, and urinary oxalate excretion.

Acknowledgments

The authors thank the study participants. This work was supported by Grants DK73381, DK59583, DK70756, CA87969, CA55075, and CA50385 from the National Institutes of Health.

Disclosures

Dr. Taylor has received consulting fees from Altus Pharmaceuticals, Inc.

References

1. Coe FL, Parks JH, Asplin JR: The pathogenesis and treatment of kidney stones. *N Engl J Med* 327: 1141–1152, 1992
2. Robertson WG, Scurr DS, Bridge CM: Factors influencing crystallization of calcium oxalate in urine: a critique. *J Crystal Growth* 53: 182, 1981
3. Curhan GC, Taylor EN: 24-h uric acid excretion and the risk of kidney stones. *Kidney Int* 73: 489–496, 2008
4. Hess B: Nutritional aspects of stone disease. *Endocrinol Metab Clin North Am* 31: 1017–1030, 2002
5. Hagler L, Herman RH: Oxalate metabolism. I. *Am J Clin Nutr* 26: 758–765, 1973
6. Menon M, Mahle CJ: Oxalate metabolism and renal calculi. *J Urol* 127: 148–151, 1982
7. Holmes RP, Goodman HO, Assimos DG: Contribution of dietary oxalate to urinary oxalate excretion. *Kidney Int* 59: 270–276, 2001
8. Hesse A, Schneeberger W, Engfeld S, von Unruh GE, Sauerbruch T: Intestinal hyperabsorption of oxalate in calcium oxalate stone formers: application of a new test with [13C2]oxalate. *J Am Soc Nephrol* 10[Suppl 14]: S329–S333, 1999
9. Voss S, Hesse A, Zimmermann DJ, Sauerbruch T, von Unruh GE: Intestinal oxalate absorption is higher in idiopathic calcium oxalate stone formers than in healthy controls: measurements with the [(13)C2]oxalate absorption test. *J Urol* 175: 1711–1715, 2006
10. Holmes RP, Assimos DG: The impact of dietary oxalate on kidney stone formation. *Urol Res* 32: 311–316, 2004
11. Traxer O, Huet B, Poindexter J, Pak CY, Pearle MS: Effect of ascorbic acid consumption on urinary stone risk factors. *J Urol* 170: 397–401, 2003
12. Lemann J Jr, Pleuss J, Worcester E, Hornick L, Schrab D, Hoffman R: Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. *Kidney Int* 49: 200–208, 1996
13. Siener R, Ebert D, Nicolay C, Hesse A: Dietary risk factors for hyperoxaluria in calcium oxalate stone formers. *Kidney Int* 63: 1037–1043, 2003
14. Holmes RP, Assimos DG: Glyoxylate synthesis, and its modulation and influence on oxalate synthesis. *J Urol* 160: 1617–1624, 1998
15. Holmes R, Kennedy M: Estimation of the oxalate content of foods and daily oxalate intake. *Kidney Int* 57: 1662–1667, 2000
16. Taylor EN, Curhan GC: Oxalate intake and the risk for nephrolithiasis. *J Am Soc Nephrol* 18: 2198–2204, 2007
17. Willett WC, Stampfer MJ: Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 124: 17–27, 1986
18. Willett WC: *Nutritional Epidemiology,* New York, NY, Oxford University Press, 1998
19. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE: Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 122: 51–65, 1985
20. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC: Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 135: 1114–1126, 1992
21. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC: Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1: 466–473, 1990
22. Colditz G, Marin P, Stampfer M, Willett W, Sampson L, Rosner B, Hennekens C, Speizer R: Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 123: 894–900, 1986
23. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB: Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* 161: 1542–1548, 2001
24. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338: 774–778, 1991
25. Curhan GC, Willett WC, Speizer FE, Stampfer MJ: Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int* 59: 2290–2298, 2001
26. Taylor EN, Stampfer MJ, Curhan GC: Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol* 15: 3225–3232, 2004
27. Taylor EN, Stampfer MJ, Curhan GC: Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 68: 1230–1235, 2005
28. von Unruh GE, Bell AE, Hesse A: Effect of oxalate test dose size on absolute and% oxalate absorption. *Isotopes Environ Health Stud* 42: 107–112, 2006
29. Zimmermann DJ, Hesse A, von Unruh GE: Influence of a high-oxalate diet on intestinal oxalate absorption. *World J Urol* 23: 324–329, 2005
30. von Unruh GE, Voss S, Sauerbruch T, Hesse A: Reference range for gastrointestinal oxalate absorption measured with a standardized [13C2]oxalate absorption test. *J Urol* 169: 687–690, 2003
31. Hess B, Jost C, Zipperle L, Takkinen R, Jaegar P: High-calcium intake abolishes hyperoxaluria and reduces uri-

nary crystallization during a 20-fold normal oxalate load in humans. *Nephrol Dial Transplant* 13: 2241–2247, 1998
32. Nguyen NU, Dumoulin G, Henriet MT, Regnard J: Increase in urinary calcium and oxalate after fructose infusion. *Horm Metab Res* 27: 155–158, 1995
33. Rofe AM, James HM, Bais R, Conyers RA: Hepatic oxalate production: the role of hydroxypyruvate. *Biochem Med Metab Biol* 36: 141–150, 1986
34. Rofe AM, James HM, Bais R, Edwards JB, Conyers RA: The production of (14C) oxalate during the metabolism of (14C) carbohydrates in isolated rat hepatocytes. *Aust J Exp Biol Med Sci* 58: 103–116, 1980
35. Taylor EN, Curhan GC: Fructose consumption and the risk of kidney stones. *Kidney Int* 73: 207–212, 2007
36. Meschi T, Maggiore U, Fiaccadori E, Schianchi T, Bosi S, Adorni G, Ridolo E, Guerra A, Allegri F, Novarini A, Borghi L: The effect of fruits and vegetables on urinary stone risk factors. *Kidney Int* 66: 2402–2410, 2004
37. Knight J, Jiang J, Assimos DG, Holmes RP: Hydroxyproline ingestion and urinary oxalate and glycolate excretion. *Kidney Int* 70: 1929–1934, 2006
38. Holmes RP, Ambrosius WT, Assimos DG: Dietary oxalate loads and renal oxalate handling. *J Urol* 174: 943–947, 2005; discussion 947