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Oxalate Intake and the Risk for Nephrolithiasis

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ABSTRACT

Most kidney stones consist of calcium oxalate, and higher urinary oxalate increases the risk for calcium oxalate nephrolithiasis. However, the relation between dietary oxalate and stone risk is unclear. This study prospectively examined the relation between oxalate intake and incident nephrolithiasis in the Health Professionals Follow-up Study (n = 45,985 men), the Nurses' Health Study I (n = 92,872 older women), and the Nurses' Health Study II (n = 101,824 younger women). Food frequency questionnaires were used to assess oxalate intake every 4 yr. Cox proportional hazards regression was used to adjust for age, body mass index, thiazide use, and dietary factors. A total of 4605 incident kidney stones were documented over a combined 44 yr of follow-up. Mean oxalate intakes were 214 mg/d in men, 185 mg/d in older women, and 183 mg/d in younger women and were similar in stone formers and non–stone formers. Spinach accounted for >40% of oxalate intake. For participants in the highest compared with lowest quintile of dietary oxalate, the relative risks for stones were 1.22 (95% confidence interval [CI] 1.03 to 1.45; P = 0.01 for trend) for men and 1.21 (95% CI 1.01 to 1.44; P = 0.05 for trend) for older women. Risk was higher in men with lower dietary calcium (P = 0.08 for interaction). The relative risks for participants who ate eight or more servings of spinach per month compared with fewer than 1 serving per month were 1.30 (95% CI 1.08 to 1.58) for men and 1.34 (95% CI 1.10 to 1.64) for older women. Oxalate intake and spinach were not associated with risk in younger women. These data do not implicate dietary oxalate as a major risk factor for nephrolithiasis.

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Kidney stones are common, costly, and painful. The lifetime prevalence of symptomatic nephrolithiasis is approximately 10% in men and 5% in women,[1,2] and more than $2 billion is spent on treatment each year.[3,4] Approximately 80% of kidney stones contain calcium, and the majority of calcium stones consist primarily of calcium oxalate.[5] Small increases in urinary oxalate can have a major effect on calcium oxalate crystal formation,[6] and higher levels of urinary oxalate are a major risk factor for the formation of calcium oxalate kidney stones.[5,7] 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.[8]

However, the role of dietary oxalate in the pathogenesis of calcium oxalate nephrolithiasis is unclear.[9] Uncertainty about the impact of dietary oxalate on stone risk centers around the contribution of oxalate intake to urinary oxalate excretion. A large amount of urinary oxalate is derived from the endogenous metabolism of glycine, glycolate, hydroxyproline, and dietary vitamin C,[10,11] and the proportion of urinary oxalate derived from dietary oxalate is unclear (estimates range from 10 to 50%[12]). Studies of dietary oxalate and stone risk also must account for the intake of other dietary factors. For example, the intake of calcium and magnesium may modulate the intestinal absorption of dietary oxalate.[9] Observational data showing an inverse relation between dietary calcium and the

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risk for incident kidney stones[13–15] suggested that dietary calcium may bind to oxalate in the gut, thereby limiting intestinal oxalate absorption (and subsequent urinary oxalate excretion). Indeed, the inhibitory effect of calcium ingestion on urinary oxalate excretion has been demonstrated in oxalate loading studies.[16–18] Magnesium intake may also decrease urinary oxalate in a similar manner.[19–21]

To examine the relation between oxalate intake and the incidence of kidney stones, we conducted a prospective study of three large cohorts: the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Studies I and II (NHS I and NHS II).

RESULTS

During a combined 44 yr of follow-up, we documented 4605 new symptomatic kidney stones in the three cohorts. In HPFS (men), NHS I (older women), and NHS II (younger women), there were 1627, 1414, and 1564 incident kidney stones, respectively.

Table 1 displays mean oxalate intake for HPFS and NHS I in 1994 and for NHS II in 1995. In each cohort, there were no substantial changes in oxalate intake over time. On average, men without kidney stones consumed 214 mg/d oxalate (median 191 mg; 10th to 90th percentile range 106 to 329 mg), older women without kidney stones consumed 185 mg/d oxalate (median 165 mg; 10th to 90th percentile range 87 to 287 mg), and younger women without kidney stones consumed 183 mg/d oxalate (median 158 mg; 10th to 90th percentile range 86 to 293 mg). There was no statistically significant difference in oxalate intake between participants with and without kidney stones.

The main sources of dietary oxalate were vegetables, fruits, nuts, and grains. The 10 foods that contribute most to total oxalate intake are listed in Table 2. Many foods that are high in oxalate, such as rhubarb, did not contribute substantially to oxalate intake because they were consumed relatively infrequently. In each cohort, spinach was the highest contributor to total oxalate intake. Consumption of spinach (cooked plus raw) constituted 40.4% of oxalate intake in men, 44.2% of oxalate intake in older women, and 42.3% of oxalate intake in younger women. Consumption of potatoes (not mashed or French fried) constituted 10.2% of oxalate intake in men, 11.1% of oxalate intake in older women, and 9.9% of oxalate intake in younger women. All other foods contributed <5% to oxalate intake.

After adjustment for age, oxalate intake was inversely associated with the risk for incident kidney stones in all three cohorts (Table 3). However, after multivariate adjustment, oxalate intake was associated with a modest increase in risk in HPFS and NHS I. The multivariate relative risk for men in the highest as compared with lowest quintile of dietary oxalate was 1.22 (95% confidence interval [CI] 1.03 to 1.45; $P = 0.01$ for trend) and the multivariate relative risk for older women was 1.21 (95% CI 1.01 to 1.44; $P = 0.05$ for trend). After multivariate adjustment, no association with risk was observed in younger women. We also evaluated kidney stone risk associated with extreme categories, rather than quintiles, of oxalate intake. The multivariate relative risk for men who consumed >350 mg/d oxalate (median intake 445 mg) compared with <100 mg/d (median intake 87 mg) was 1.35 (95% CI 1.05 to 1.73; $P = 0.009$ for trend). The multivariate relative risks in identical categories for older and younger women were 1.28 (95% CI 0.97 to 1.68; $P = 0.10$ for trend) and 1.11 (95% CI 0.86 to 1.45; $P = 0.28$ for trend), respectively.

Because of the importance of spinach as a contributor to total oxalate intake, we evaluated the association between spinach intake and kidney stone risk (Table 4). Spinach contains many dietary factors that are associated with risk (*e.g.*, calcium, potassium, magnesium, vitamin C), thereby complicating the interpretation of multivariate stone risk that is associated with spinach intake. However, spinach contributed to <2% of calcium, potassium, magnesium, and vitamin C intake in each cohort. Total spinach intake was associated with risk in men

Table 1. Oxalate intake (mg/d) in men (HPFS), older women (NHS I), and younger women (NHS II)[a]

Parameter	Stone Formers	Non–Stone Formers	*P*
HPFS			
mean (SD)	215 (117)	214 (121)	0.84
median	194	191	
10th to 90th percentile range	107 to 342	106 to 329	
NHS I			
mean (SD)	184 (109)	185 (112)	0.94
median	166	165	
10th to 90th percentile range	86 to 291	87 to 287	
NHS II			
mean (SD)	179 (121)	183 (121)	0.45
median	151	158	
10th to 90th percentile range	81 to 283	86 to 293	

[a]For illustrative purposes, oxalate values were derived from responses to the 1994 (men and older women) and 1995 (younger women) dietary questionnaires. Updated period-specific values were used for prospective analyses. Oxalate values were adjusted for total caloric intake. HPFS, Health Professionals Follow-up Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II.

Table 2. Foods that contribute to oxalate intake in men (HPFS), older women (NHS I), and younger women (NHS II)[a]

HPFS		NHS I		NHS II	
Food	%	Food	%	Food	%
Cooked spinach	23.1	Cooked spinach	25.8	Cooked spinach	22.0
Raw spinach	17.3	Raw spinach	18.4	Raw spinach	20.3
Potatoes (whole)	10.2	Potatoes (whole)	11.1	Potatoes (whole)	9.9
Cold cereal	4.4	Cold cereal	4.3	Cold cereal	3.8
Oranges	2.9	Oranges	2.5	French fries	2.5
French fries	1.9	Coffee	1.7	Oranges	2.0
Mixed nuts[b]	1.7	Cooked carrots	1.7	Pasta	2.0
Navy beans (canned)	1.7	Tea	1.6	Pasta sauce[d]	1.9
Cookies[c]	1.6	Cookies[c]	1.5	English muffins	1.7
Peanuts	1.6	Pasta sauce[d]	1.4	Coffee	1.7

[a]Expressed as percentage of total oxalate intake. Based on oxalate content and frequency of consumption. For illustrative purposes, values were derived from responses to the 1994 (men and older women) and 1995 (younger women) dietary questionnaires.
[b]With peanuts.
[c]Chocolate chip.
[d]Marinara.

Table 3. RR for incident kidney stones in men (HPFS), older women (NHS I), and younger women (NHS II) by quintile of oxalate intake[a]

Parameter	Quintile					*P* for Trend
	1	2	3	4	5	
HPFS						
quintile median (mg/d)	106	149	191	236	328	
cases	363	317	325	313	309	
person-years	105,806	106,298	107,393	108,200	107,788	
age-adjusted RR (95% CI)	1.0	0.89 (0.76 to 1.03)	0.89 (0.77 to 1.04)	0.85 (0.73 to 0.99)	0.85 (0.73 to 0.99)	0.04
multivariate RR (95% CI)[b]	1.0	1.01 (0.86 to 1.17)	1.07 (0.92 to 1.25)	1.10 (0.94 to 1.29)	1.22 (1.03 to 1.45)	0.01
NHS I						
quintile median (mg/d)	87	127	164	205	287	
cases	312	279	304	250	269	
person-years	254,953	257,271	259,528	259,712	258,882	
age-adjusted RR (95% CI)	1.0	0.89 (0.76 to 1.05)	0.96 (0.82 to 1.12)	0.79 (0.67 to 0.93)	0.85 (0.72 to 1.00)	0.03
multivariate RR (95% CI)[b]	1.0	1.02 (0.86 to 1.20)	1.16 (0.99 to 1.36)	1.03 (0.87 to 1.23)	1.21 (1.01 to 1.44)	0.05
NHS II						
quintile median (mg/d)	85	117	157	202	293	
cases	365	340	296	286	277	
person-years	169,306	168,806	169,837	169,964	169,674	
age-adjusted RR (95% CI)	1.0	0.95 (0.82 to 1.10)	0.83 (0.71 to 0.96)	0.80 (0.69 to 0.94)	0.79 (0.67 to 0.92)	0.001
multivariate RR (95% CI)[b]	1.0	1.03 (0.88 to 1.20)	0.96 (0.82 to 1.13)	1.00 (0.85 to 1.18)	1.06 (0.89 to 1.27)	0.57

[a]CI, confidence interval; RR, relative risk.
[b]Results are adjusted for age; body mass index (BMI; six categories); use of thiazide diuretics (yes or no); fluid intake (in quintiles); alcohol use (seven categories); calcium supplement use (four categories); and dietary intake of animal protein, calcium, potassium, sodium, phytate, vitamin C, and magnesium (all in quintiles).

and older women but not in younger women. The multivariate relative risk for men who consumed eight or more servings of spinach per month compared with fewer than one serving was 1.30 (95% CI 1.08 to 1.58), and the multivariate relative risk for older women was 1.34 (95% CI 1.10 to 1.64).

We also tested the hypothesis that the relation between dietary oxalate and stone risk varied by calcium intake. Because we did not have data about the timing of calcium supplement ingestion in relation to food intake, we performed these stratified analyses in participants who did not consume calcium supplements. In men with dietary calcium below the median (755 mg/d), the multivariate relative risk in the highest as compared with lowest quintile of dietary oxalate was 1.46 (95% CI 1.11 to 1.93; $P = 0.008$ for trend). In men with calcium intake at or above the median, the multivariate relative risk in the highest as compared with lowest quintile of dietary oxalate was 0.83 (95% CI 0.61 to 1.13; $P = 0.31$ for trend). The P value for interaction between oxalate and calcium intake was 0.08. In contrast, the relation between oxalate intake and stone risk did not vary by calcium intake in older or younger women.

Stratified analyses of the relation between oxalate intake and risk evaluating the lowest quintile of calcium intake, rather than median calcium intake, did not result in higher estimates

Table 4. Total spinach intake and the relative risk for incident kidney stones in men (HPFS), older women (NHS I), and younger women (NHS II)

Parameter	Spinach Servings		
	<1/mo	1 to 7/mo	≥8/mo
HPFS			
cases	541	936	150
person-years	174,589	307,680	53,214
age-adjusted RR (95% CI)	1.0	0.95 (0.86 to 1.06)	0.89 (0.75 to 1.07)
multivariate RR (95% CI)[a]	1.0	1.11 (0.99 to 1.24)	1.30 (1.08 to 1.58)
NHS I			
cases	468	807	139
person-years	411,253	753,777	125,316
age-adjusted RR (95% CI)	1.0	0.92 (0.82 to 1.03)	0.95 (0.78 to 1.14)
multivariate RR (95% CI)[a]	1.0	1.09 (0.97 to 1.23)	1.34 (1.10 to 1.64)
NHS II			
cases	684	766	114
person-years	328,525	445,464	73,598
age-adjusted RR (95% CI)	1.0	0.84 (0.76 to 0.93)	0.76 (0.62 to 0.93)
multivariate RR (95% CI)[a]	1.0	0.96 (0.87 to 1.07)	1.00 (0.81 to 1.24)

[a]Results adjusted for age; BMI (six categories); use of thiazide diuretics (yes or no); fluid intake (in quintiles); alcohol use (seven categories); calcium supplement use (four categories); and dietary intake of animal protein, calcium, potassium, sodium, phytate, vitamin C, and magnesium (all in quintiles).

of risk. Finally, the relation between oxalate intake and risk did not vary by magnesium intake or body size.

DISCUSSION

In men (HPFS) and older women (NHS I), oxalate intake and spinach consumption were associated with small increases in the risk for incident kidney stone formation. The magnitude of risk was higher in men who consumed lower intakes of dietary calcium. In contrast to men and older women, we observed no relation between dietary oxalate or spinach and stone risk in younger women (NHS II). Of note, we have reported previously that the relation between some dietary factors and stone risk varies by cohort. For instance, potassium intake is inversely associated with risk in men and older women but not in younger women.[13–15] It is possible that the association between oxalate intake and stone risk varies by age, but there were not enough older women in NHS II to permit age-stratified analyses.

The modest associations between dietary oxalate and stone risk that were observed in our study may reflect the primacy of endogenous oxalate synthesis in the pathogenesis of hyperoxaluria. The proportion of urinary oxalate that is derived from dietary oxalate is unclear: estimates range from 10 to 50%.[12] However, it is well established that a large proportion of urinary oxalate is derived from the endogenous metabolism of glycine, glycolate, hydroxyproline, and dietary vitamin C.[10,11] A recent metabolic study compared a controlled diet with 25% of protein from gelatin (2.75 g of hydroxyproline) with the same diet except with 25% of protein from whey (containing no hydroxyproline).[22] The diet that was high in hydroxyproline increased urinary oxalate excretion by 42%. Another metabolic trial demonstrated that 1000 mg of supplemental vitamin C consumed twice daily increased urinary oxalate excretion by 20 to 33%.[23]

To our knowledge, only two previous studies that used direct analytical techniques to measure food oxalate attempted to quantify the oxalate content of the typical Western diet. One study consisted of five healthy individuals (mean age 29 yr), and the mean oxalate intake, as measured by a 3-d dietary record, was 152 mg/d.[24] The other study consisted of 186 calcium oxalate stone formers (mean age 48 yr), divided into two groups on the basis of urinary oxalate excretion. The difference in oxalate intake between the two groups was not statistically significant, and the mean intakes, as measured by a 24-h dietary record, were 101 and 130 mg/d.[25] No analysis was performed to determine whether oxalate intake varied by gender. Our study suggests that oxalate intakes in free-living Western populations are substantially higher and that men consume more oxalate than women.

Our data do not exclude an important role for dietary oxalate in the pathogenesis of calcium oxalate kidney stone formation. Although oxalate intake did not differ substantially between stone formers and non–stone formers, it is reasonable to speculate that stone formers might absorb more dietary oxalate than their non–stone-forming counterparts. Indeed, increased absorption of dietary oxalate may be observed in up to one third of patients with calcium oxalate nephrolithiasis.[12] Another study found that mean oxalate absorption in normal volunteers was 8%, compared with 10.2% in a group of calcium oxalate stone formers.[26] Some data suggest that differential rates of colonization by *Oxalobacter formigenes*, an enteric oxalate-degrading organism, may be responsible for such variation.[27–29] Finally, genetic difference between individuals might result in differences in intestinal oxalate absorption.[9]

A limitation to this study is that the bioavailability of dietary oxalate may vary substantially by food type. For example, bioavailability (as measured by the increase in urinary oxalate excretion 6 to 8 h after food ingestion) ranges from 0.6 to 2.4%

for spinach and may be as high as 4% for rhubarb.[30–32] Marked differences in oxalate bioavailability between frequently consumed foods in our study would introduce error into our measurements of dietary oxalate exposure and would attenuate the observed associations between dietary oxalate and stone risk. Although some authors have proposed measuring soluble, instead of total, oxalate food content as a proxy for absorbable oxalate, this contention is controversial.[9] There is no accepted assay, beyond oxalate loading studies, to determine the oxalate bioavailability of individual foods.

Another limitation is that we do not have stone composition reports or 24-h urine collections from all of the stone formers in our cohorts. However, the majority of stone composition reports in each cohort show kidney stones that contained ≥50% calcium oxalate. Furthermore, urinary oxalate is a major risk factor for kidney stone formation in these cohorts.[7] Finally, only a small proportion of our study population is nonwhite, and we do not have data on stone formation in men who are younger than 40 yr.

CONCLUSION

Our data do not support the contention that dietary oxalate is a major risk factor for incident kidney stones. The risk that was associated with oxalate intake was modest even in individuals who consumed diets that were relatively low in calcium. We hope that our study encourages additional research into the relations between dietary oxalate, other dietary factors, endogenous oxalate production, urinary oxalate, and kidney stone formation.

CONCISE METHODS

Study Population

HPFS.

In 1986, 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians between the ages of 40 and 75 yr completed and returned an initial questionnaire that provided detailed information on diet, medical history, and medications. This cohort, like NHS I and NHS II, is followed by biennial mailed questionnaires, which include inquiries about newly diagnosed diseases such as kidney stones. We limited the analysis to men who completed at least one dietary questionnaire and excluded participants with a history of kidney stones before 1986. A total of 45,985 men remained in the study group.

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. Because we first asked NHS I participants about their lifetime history of kidney stones in 1992, this analysis was limited to women who answered questionnaires in 1992 or later. For this study, we started follow-up in 1984, because before that date we lacked information on phytate intake. After exclusion of women with kidney stones before 1984, our study population included 92,872 women.

NHS II.

In 1989, 116,671 female registered nurses between the ages of 25 and 42 yr enrolled in NHS II by completing and returning an initial questionnaire. Dietary information was first collected from this cohort in 1991. We limited the analysis to women who completed at least one dietary questionnaire and excluded participants with a history of kidney stones before 1991. A total of 101,824 women remained in the study group.

Assessment of Diet and Measurement of Oxalate

The baseline semiquantitative food frequency questionnaires (FFQ) for this study (mailed to HPFS in 1986, to NHS I in 1984, and to NHS II in 1991) asked about the annual average use of more than 130 foods and beverages. Subsequently, a version of this FFQ has been mailed to study participants every 4 yr.

The oxalate content of the majority of foods on the FFQ, as well as frequently consumed write-in foods, was measured by capillary electrophoresis in the laboratory of Dr. Ross Holmes. This assay has been described in detail elsewhere.[24] Each item of food was subject to at least three measurements, and the final value was obtained by arithmetic mean. Commercial preparations (packaged, canned, etc.) were purchased from different lots, and fresh produce was purchased on three different days spaced at least 1 wk apart.

The resulting oxalate food database contained 283 direct values from analysis, nine calculated values, 123 values imputed from analyzed food, and 59 values imputed from recipe compilations. Margarines were assigned zero on the basis of a former analysis that showed no oxalate detection. Cereals were added to the database using 35 direct values from analysis and 18 imputed values from other analyzed cereals.

Intake of oxalate and other dietary factors was computed from the reported frequency of consumption of each specified unit of food and, with the exception of oxalate, from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake to determine the nutrient composition of the diet independent of the total amount of food eaten. Adjustment was performed using a regression model, with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable.[33,34]

The intake of supplements (*e.g.*, calcium, vitamin C) in multivitamins or isolated form was determined by the brand, type, and frequency of reported use. The reproducibility and validity of the FFQ in the HPFS and NHS I have been documented.[35,36]

Assessment of Nondietary Covariates

For each cohort, information on age, weight, and height was obtained on the baseline questionnaire, and age and weight were updated every 2 yr. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Information on thiazide diuretics was updated every 2 yr in HPFS and NHS II. In NHS I, thiazide use was determined in 1980 and 1982 and then every 6 yr until 1994, when biennial updates started.

Outcomes and Their Measurement

The primary outcome was an incident kidney stone accompanied by pain or hematuria. The participants reported on the interval diagnosis of kidney stones every 2 yr. Any study participant who reported a new kidney stone on the biennial questionnaire was sent an additional questionnaire to determine the date of occurrence and the symptoms from the stone. In HPFS, we obtained medical records from 582 men who reported a kidney stone, and the diagnosis was confirmed in 95%. A total of 148 records contained a stone composition report, and 127 (86%) men had a stone that contained ≥50% calcium oxalate. In NHS I, we obtained medical records from 194 women who reported a kidney stone, and 96% of the records confirmed the diagnosis. A total of 78 records contained a stone composition report, and 60 (77%) women had a stone that contained ≥50% calcium oxalate. In NHS II, we obtained medical records from 858 women who reported a kidney stone, and 98% of the records confirmed the diagnosis. A total of 243 records contained a stone composition report, and 191 (79%) women had a stone that contained ≥50% calcium oxalate.

Statistical Analyses

The study design was prospective; information on diet was collected before the diagnosis of the kidney stone. The relative risk was used as the measure of association between oxalate intake and incident kidney stones. Oxalate intake was divided into quintiles, and the lowest quintile served as the referent group. The Mantel extension test was used to evaluate linear trends across categories of intake.

Dietary exposures were updated every 4 yr. We allocated person-months of follow-up according to exposure status at the start of each follow-up period. When complete information on diet was missing at the start of a time period, the subject was excluded for that time period. For HPFS, person-months of follow-up were counted from the date of the return of the 1986 questionnaire to the date of a kidney stone or death or to January 31, 2002, whichever came first. For NHS I, person-months of follow-up were counted from the date of the return of the 1984 questionnaire to the date of a kidney stone or death or to May 31, 2002. For NHS II, person-months of follow-up were counted from the date of the return of the 1991 questionnaire to the date of a kidney stone or death or to May 31, 2001.

We adjusted our analyses for potentially confounding variables using Cox proportional hazards regression. The confounding variables considered were age (continuous); body mass index (six categories); alcohol intake (seven categories); the use of thiazide diuretics (yes or no); supplemental calcium use (four categories); and the intake of fluid, potassium, sodium, animal protein, phosphorous, magnesium, sucrose, vitamin C, vitamin B_6, phytate, vitamin D, and dietary calcium (quintile groups). We calculated 95% CI for all relative risks. All *P* values are two tailed.

All data were analyzed by using SAS software, version 9.1 (SAS Institute, Cary, NC). The research protocol for this study was reviewed and approved by the institutional review board of Brigham and Women's Hospital.

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DISCLOSURES

None.

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