Dietary Calcium from Dairy and Nondairy Sources, and Risk of Symptomatic Kidney Stones

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Purpose: Because of high correlations between dairy intake and total dietary calcium, previously reported associations between lower calcium intake and increased kidney stone risk represent de facto associations between milk products and risk. We examined associations between dietary calcium from nondairy and dairy sources, and symptomatic nephrolithiasis.

Materials and Methods: We performed prospective studies in the Health Professionals Follow-up Study (HPFS) in 30,762 men, and in the Nurses' Health Study (NHS) I and II in 94,164 and 101,701 women, respectively. We excluded men 60 years old or older because we previously reported inverse associations between calcium intake and risk only in men younger than 60 years. Food frequency questionnaires were used to assess calcium intake every 4 years. We used Cox proportional hazards regression to adjust for age, body mass index, supplemental calcium, diet and other factors.

Results: We documented 5,270 incident kidney stones during the combined 56 years of followup. In participants in the highest vs the lowest quintile of nondairy dietary calcium the multivariate relative risk of kidney stones was 0.71 (95% CI 0.56–0.92, p for trend 0.007) in HPFS, 0.82 (95% CI 0.69–0.98, p trend 0.08) in NHS I and 0.74 (95% CI 0.63–0.87, p trend 0.002) in NHS II. When comparing the highest to the lowest quintile of dairy calcium, the multivariate relative risk was 0.77 (95% CI 0.63–0.95, p trend 0.01) for HPFS, 0.83 (95% CI 0.69–0.99, p trend 0.05) for NHS I and 0.76 (95% CI 0.65–0.88, p trend 0.001) for NHS II.

Conclusions: Higher dietary calcium from nondairy or dairy sources is independently associated with a lower kidney stone risk.

Key Words: kidney, kidney calculi, calcium, diet, risk

Abbreviations and Acronyms

BMI = body mass index

FFQ = food-frequency questionnaire

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Lower dietary calcium is an established risk factor for calcium kidney stone formation. In observational studies we and others previously reported prospective, independent associations between lower dietary calcium and an increased risk of incident kidney stones.[1–4] In a randomized trial of 120 men with calcium oxalate stone disease and idiopathic hypercalciuria Borghi et al compared the effects of a low calcium diet (400 mg per day) and a higher calcium diet (1,200 mg per day) that was also restricted in sodium (1,200 mg per day) and animal protein (52 gm per day).[5] Study participants on the higher calcium diet had a 51% lower risk of recurrent nephrolithiasis than their low calcium

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counterparts. The mechanism by which higher calcium intake may decrease the stone risk is unclear. More calcium in the intestinal lumen may possibly result in lower intestinal absorption of oxalate and, thus, lower urinary excretion of oxalate.[6,7]

Despite these data, the relations between dietary calcium and kidney stone formation require elucidation. Because of the large contribution of milk products to nonsupplemental calcium intake in Western populations, large-scale observational studies to date of associations between dietary calcium and stone risk have to a large extent delineated associations between dairy intake and risk. Furthermore, in contrast to dietary calcium, higher supplemental calcium intake is associated with an increased rather than a decreased risk of kidney stone formation.[1,8] Taken together, these points suggest the important possibility that milk products may contain an unknown factor that inhibits calcium stone formation. To our knowledge no group to date has examined the association between nondairy dietary calcium and kidney stone risk.

To examine the independent associations between dietary calcium from nondairy and dairy sources, and the risk of incident symptomatic kidney stones, we performed prospective analyses in the 3 large cohorts of HPFS, and NHS I and II.

MATERIALS AND METHODS

Study Populations

A total of 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists and veterinarians between ages 40 and 75 years enrolled in HPFS in 1986 by completing and returning an initial questionnaire providing detailed information on diet, medical history and medication. Like NHS I and II, the HPFS cohort is followed by biennial mailed questionnaires, which include inquiries on newly diagnosed diseases such as kidney stones. We limited analysis to men who completed at least 1 dietary questionnaire and excluded participants with a history of kidney stones before 1986. We also excluded men 60 years old or older because we previously reported inverse associations between calcium intake and stone risk only in HPFS participants younger than 60 years.[9] A total of 30,762 men remained in the study group.

A total of 121,700 female registered nurses between ages 30 and 55 years enrolled in NHS I in 1976. Since we first asked NHS I participants about their lifetime history of kidney stones in 1992, the current analysis was limited to women who answered questionnaires in 1992 or later. For this study we started followup in 1986. After excluding women with kidney stones before 1986, our study population included 94,164 NHS I participants.

A total of 116,430 female registered nurses between ages 25 and 42 years enrolled in NHS II in 1989. Dietary information was first collected from this cohort in 1991. We limited analysis to women who completed at least 1 dietary questionnaire and excluded participants with a history of kidney stones before 1991. A total of 101,701 NHS II participants remained in the study group.

Assessments

Diet. The baseline semiquantitative FFQs asked about the annual average use of more than 130 individual foods and 22 beverages. Subsequently, a version of this FFQ has been mailed to study participants every 4 years. The intake of dietary factors was calculated from the reported frequency of consumption of each specified unit of food and, except oxalate, from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. The oxalate content of most foods on the FFQ as well as frequently consumed foods written in, was measured by capillary electrophoresis, as previously described in detail.[10,11] 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.[12,13]

The intake of mineral and vitamin supplements, such as calcium and vitamin D, in multivitamin or isolated form was determined by the brand, type and frequency of reported use. The reproducibility and validity of the FFQs were previously documented in HPFS and NHS I.[14,15]

Nondietary covariates. For each cohort information on age, weight and height was obtained on the baseline questionnaire. Age and weight were updated every 2 years. BMI was calculated as weight in kg divided by height in m^2. Information on thiazide diuretics was updated every 2 years in HPFS and NHS II. In NHS I thiazide use was determined in 1980, 1982 and every 6 years until 1994, when biennial updates started.

Incident kidney stones. The primary outcome was an incident kidney stone accompanied by pain or hematuria. Participants reported the interval diagnosis of kidney stones every 2 years. 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 stone symptoms.

In HPFS we obtained the medical records of 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 men (86%) had a stone that contained 50% or greater calcium oxalate. In NHS I we obtained the medical records of 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 women (77%) had a stone that contained 50% or greater calcium oxalate. In NHS II we obtained the medical records of 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 women (79%) had a stone that contained 50% or greater calcium oxalate.

Statistical Analysis

The study design was prospective with information on diet collected before the kidney stone diagnosis. Relative risk was used as the measure of association between dairy

and nondairy dietary calcium, and incident kidney stones. Dairy and nondairy dietary calcium were divided into quintiles and the lowest quintiles served as the referent. The Mantel extension test was used to evaluate linear trends across intake categories.

Dietary exposure was updated every 4 years. We allocated person-time of followup according to exposure status at the start of each followup period. If complete information on diet was missing at the start of a period, the participant was excluded from that period. For HPFS person-time was counted from the date of the return of the 1986 questionnaire to the date of a kidney stone or death or to January 31, 2006, whichever was first. For NHS I person-time was counted from the date of the return of the 1986 questionnaire to the date of a kidney stone or death, or to May 31, 2006. For NHS II person-time was counted from the date of the return of the 1991 questionnaire to the date of a kidney stone or death, or to May 31, 2007.

We adjusted our analyses for potentially confounding variables using Cox proportional hazards regression. The confounding variables considered were age (continuous), BMI (6 categories), diabetes history, hypertension history, thiazide diuretic use (yes or no), family history of kidney stones (yes or no in HPFS and NHS II), fluid intake (quintiles), alcohol intake (7 categories), calcium supplement use (0, 1 to 100, 101 to 500 and 500 or greater mg per day), and intake of animal protein, potassium, sodium, vitamin C, oxalate, magnesium and caffeine (quintiles). We calculated the 95% CI for all relative risks and all p values are 2-tailed.

Data were analyzed using SAS®, version 9.2. The research protocol for this study was reviewed and approved by the Brigham and Women's Hospital institutional review board.

Table 1. *Age standardized characteristics of men younger than 60 years in HPFS, and women in NHS I and NHS II by baseline energy adjusted nondairy dietary calcium*

	Quintile					p for Trend
	1	2	3	4	5	
			HPFS			
Mean age*	48.2	48.6	49.1	49.4	49.2	<0.001
Mean BMI (kg/m^2)*	25.6	25.6	25.6	25.5	25.3	<0.001
% Hypertension	16.7	16.7	16.2	16.4	16.6	0.66
% Thiazide	5.8	6.0	5.4	6.0	5.3	0.22
% Diabetes mellitus	0.9	1.5	2.0	2.2	2.7	<0.001
Mean calcium (mg/day):*						
Supplemental†	56	70	79	99	134	<0.001
Dairy	475	491	474	464	432	<0.001
Nondairy	238	289	318	351	434	<0.001
			NHS I			
Mean age*	51.9	52.4	52.7	52.9	53.1	<0.001
Mean BMI (kg/m^2)*	24.7	25.0	25.2	25.5	25.7	<0.001
% Hypertension	23.2	23.2	24.4	26.0	27.0	<0.001
% Thiazide	11.0	11.9	12.5	13.3	14.9	<0.001
% Diabetes mellitus	1.8	2.6	3.3	4.1	5.1	<0.001
Mean calcium (mg/day):*						
Supplemental†	307	336	360	381	413	<0.001
Dairy	437	452	448	437	414	<0.001
Nondairy	262	304	329	357	419	<0.001
			NHS II			
Mean age*	35.7	36.0	36.2	36.3	36.4	<0.001
Mean BMI (kg/m^2)*	24.6	24.5	24.6	24.7	24.6	0.28
% Hypertension	6.3	5.6	6.2	6.4	6.9	0.02
% Thiazide	1.3	1.5	1.8	2.0	2.0	<0.001
% Diabetes mellitus	0.5	0.7	0.9	1.1	1.5	<0.001
Mean calcium (mg/day):*						
Supplemental†	103	113	124	137	165	<0.001
Dairy	617	609	584	555	513	<0.001
Nondairy	253	302	332	364	440	<0.001

Nutrient values adjusted for caloric intake.
* Derived from 1986 HPFS and NHS I, and 1991 NHS II questionnaire responses.
† Includes calcium in multivitamin preparations.

RESULTS

During a combined 56 years of followup, we documented a total of 5,270 new symptomatic kidney stones in the 3 cohorts. In HPFS (men), NHS I (older women) and NHS II (younger women) there were 1,133, 1,806 and 2,331 incident kidney stones, respectively.

At baseline study participants with higher nondairy dietary calcium were older, more likely to have a history of diabetes and more likely to use thiazide diuretics (NHS I and NHS II only), and consume more supplemental and less dairy calcium (table 1). NHS I participants with higher nondairy dietary calcium had higher BMI and were more likely to have a history of hypertension. At baseline the fraction of dietary calcium from nondairy sources, calculated as mean nondairy dietary calcium/mean total dietary calcium, was 41% for HPFS, 46% for NHS I and 38% for NHS II. However, the Spearman correlation coefficients between energy adjusted dairy calcium and total dietary calcium were 0.95 in HPFS, 0.97 in NHS I and 0.96 in NHS II. In contrast, the correlation coefficients between energy adjusted nondairy dietary calcium and total dietary calcium were 0.23 in HPFS, 0.20 in NHS I and 0.13 in NHS II.

Higher dietary calcium from nondairy or dairy sources was independently associated with a lower risk of incident kidney stones in all 3 cohorts (table 2). The multivariate relative risk in the highest vs lowest quintile of nondairy dietary calcium was 0.71 (95% CI 0.56 to 0.92, p for trend 0.007) in HPFS, 0.82 (95% CI 0.69 to 0.98, p for trend 0.08) in NHS I and 0.74 (95% CI 0.63 to 0.87, p for trend 0.002) in NHS II. The multivariate relative risk in the highest vs lowest quintile of dairy calcium was 0.77 (95% CI 0.63 to 0.95, p for trend 0.01) in HPFS, 0.83 (95% CI 0.69 to 0.99, p for trend 0.05) in NHS I and 0.76 (95% CI 0.65 to 0.88, p for trend 0.001) in NHS II.

We also performed analyses stratified by the intake (above and below the median) of total vitamin D, total dietary calcium and oxalate. The magnitude of associations between higher nondairy dietary calcium and dairy calcium, and lower kidney stone risk were similar in participants with higher and lower vitamin D intake, higher and lower dietary calcium, and higher and lower oxalate. Additional multivariate adjustment for menopause

Table 2. *Relative risk of incident kidney stones in men younger than 60 years in HPFS, and women in NHS I and II by nondairy dietary calcium and dairy calcium quintiles*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p for Trend
			Nondairy Dietary Calcium			
HPFS:						
Median calcium (mg/day)*	262	310	345	384	460	
No. cases	280	277	229	210	137	
No. person-yrs	64,948	63,521	61,905	61,165	60,006	
Age adjusted RR (95% CI)	1.0	1.01 (0.86—1.20)	0.86 (0.72—1.03)	0.80 (0.67—0.96)	0.53 (0.43—0.65)	<0.001
Multivariate RR (95% CI)†	1.0	1.10 (0.93—1.31)	0.99 (0.82—1.20)	0.99 (0.80—1.21)	0.71 (0.56—0.92)	0.007
NHS I:						
Median calcium (mg/day)*	272	315	345	378	441	
No. cases	444	375	367	323	297	
No. person-yrs	286,868	287,835	288,285	288,964	289,611	
Age adjusted RR (95% CI)	1.0	0.85 (0.74—0.98)	0.84 (0.73—0.96)	0.74 (0.64—0.85)	0.68 (0.59—0.79)	<0.001
Multivariate RR (95% CI)†	1.0	0.89 (0.78—1.03)	0.92 (0.79—1.07)	0.85 (0.72—1.00)	0.82 (0.69—0.98)	0.08
NHS II:						
Median calcium (mg/day)*	256	302	334	371	439	
No. cases	627	462	487	397	358	
No. person-yrs	256,151	257,286	258,443	258,750	259,144	
Age adjusted RR (95% CI)	1.0	0.75 (0.66—0.84)	0.78 (0.70—0.88)	0.65 (0.57—0.73)	0.58 (0.51—0.66)	<0.001
Multivariate RR (95% CI)†	1.0	0.81 (0.72—0.92)	0.89 (0.79—1.02)	0.78 (0.67—0.90)	0.74 (0.63—0.87)	0.002
			Dairy Calcium			
HPFS:						
Median calcium (mg/day)*	151	272	385	528	839	
No. cases	252	261	214	216	190	
No. person-yrs	61,397	64,447	62,981	62,671	60,048	
Age adjusted RR (95% CI)	1.0	0.98 (0.82—1.16)	0.82 (0.69—0.99)	0.83 (0.70—1.00)	0.77 (0.64—0.93)	0.002
Multivariate RR (95% CI)†	1.0	0.95 (0.79—1.13)	0.79 (0.66—0.95)	0.80 (0.67—0.97)	0.77 (0.63—0.95)	0.01
NHS I:						
Median calcium (mg/day)*	143	266	377	523	816	
No. cases	400	411	351	363	281	
No. person-yrs	284,583	287,508	289,352	289,877	290,242	
Age adjusted RR (95% CI)	1.0	1.01 (0.88—1.16)	0.86 (0.75—1.00)	0.89 (0.77—1.03)	0.70 (0.60—0.82)	<0.001
Multivariate RR (95% CI)†	1.0	1.02 (0.89—1.18)	0.91 (0.78—1.05)	0.97 (0.84—1.13)	0.83 (0.69—0.99)	0.05
NHS II:						
Median calcium (mg/day)*	181	319	446	615	937	
No. cases	559	500	443	444	385	
No. person-yrs	254,554	256,792	258,225	259,369	260,835	
Age adjusted RR (95% CI)	1.0	0.89 (0.79—1.01)	0.79 (0.70—0.89)	0.79 (0.69—0.89)	0.68 (0.60—0.77)	<0.001
Multivariate RR (95% CI)†	1.0	0.91 (0.81—1.03)	0.83 (0.73—0.95)	0.85 (0.74—0.97)	0.76 (0.65—0.88)	0.001

* For illustrative purposes values were derived from responses to 1994 (HPFS and NHS I) and 1995 (NHS II) dietary questionnaires, while prospective analysis used updated, period specific values.
† Adjusted for age, BMI (6 categories), diabetes history, hypertension history, thiazide diuretics (yes or no), kidney stone family history (yes or no in HPFS and NHS II), fluid intake (quintiles), alcohol (7 categories), calcium supplement (4 categories), and intake of nondairy dietary or dairy calcium, animal protein, potassium, sodium, vitamin C, oxalate, magnesium and caffeine (quintiles).

as well as analysis restricted to postmenopausal women in NHS I yielded results similar to those of the primary analyses.

DISCUSSION

In men and women higher dietary calcium from nondairy or dairy sources is associated with a lower risk of incident symptomatic kidney stones. This inverse association is independent of age, body size, dietary factors, intake of fluid and supplemental calcium, thiazide use and other kidney stone risk factors.

Because of the high correlation between total dietary calcium and dairy intake in Western populations, previous large-scale observational studies of dietary calcium and kidney stone risk represent de facto studies of milk products and risk. In the randomized trial by Borghi et al comparing the effects of a higher to a low calcium diet on recurrent calcium oxalate stone formation, calcium restriction was achieved by avoiding dairy, ie milk, yogurt and cheese.[5] Our current data enable us to dismiss the important possibility that dairy products were solely responsible for previously observed associations between higher dietary calcium and a lower risk of incident kidney stones.

Our results do not provide insight into why dietary calcium may exert different effects on kidney stone risk than supplemental calcium. In these cohorts and others supplemental calcium use is associated with a nominal increase in kidney stone formation.[1,8] For example, participants in the Women's Health Initiative who received 1,000 mg supplemental calcium and 400 IU vitamin D_3 daily were 17% more likely to have a kidney stone than participants in the placebo group.[8] Since feeding studies suggest that orally administered calcium

can decrease intestinal oxalate absorption and subsequent renal oxalate excretion,[6,7] it is reasonable to speculate that the effect of supplemental calcium on kidney stone risk depends on whether supplements are received with or between meals.

Our study has limitations. 1) We did not have kidney stone composition reports from all stone formers. Thus, we could not determine whether associations between nondairy dietary calcium and risk varied by stone type. However, most stone composition reports in each cohort showed that kidney stones contained 50% or greater calcium oxalate. 2) As in any observational study, we cannot rule out the possibility of confounding by unknown or unmeasured factors associated with stone risk. 3) Data from the validated FFQ can only approximate the actual nutrient intake. However, we expect that a potential misclassification of dietary intake would be random with respect to the subsequent risk of symptomatic nephrolithiasis. 4) Our results may not be generalizable. Only a small fraction of our study population is nonwhite and we do not have data on stone formation in men younger than 40 years.

CONCLUSIONS

Regardless of source, higher dietary calcium is independently associated with a lower risk of symptomatic kidney stones in 3 large cohorts of free living individuals. Restriction of dietary calcium should not be recommended as a means of preventing calcium kidney stones.

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