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Intake of Vitamins B6 and C and the Risk of Kidney Stones in Women

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Abstract. Urinary oxalate is an important determinant of calcium oxalate kidney stone formation. High doses of vitamin B6 may decrease oxalate production, whereas vitamin C can be metabolized to oxalate. This study was conducted to examine the association between the intakes of vitamins B6 and C and risk of kidney stone formation in women. The relation between the intake of vitamins B6 and C and the risk of symptomatic kidney stones were prospectively studied in a cohort of 85,557 women with no history of kidney stones. Semiquantitative food-frequency questionnaires were used to assess vitamin consumption from both foods and supplements. A total of 1078 incident cases of kidney stones was documented during the 14-yr follow-up period. A high intake of vitamin B6 was inversely associated with risk of stone formation. After adjusting for other dietary factors, the relative risk of incident stone formation for women in the highest category of B6 intake (≥40 mg/d) compared with the lowest category (<3 mg/d) was 0.66 (95% confidence interval, 0.44 to 0.98). In contrast, vitamin C intake was not associated with risk. The multivariate relative risk for women in the highest category of vitamin C intake (≥1500 mg/d) compared with the lowest category (<250 mg/d) was 1.06 (95% confidence interval, 0.69 to 1.64). Large doses of vitamin B6 may reduce the risk of kidney stone formation in women. Routine restriction of vitamin C to prevent stone formation appears unwarranted.

The concentration of urinary oxalate is an important determinant of the risk of formation of calcium oxalate crystals, the most common component of kidney stones. The likelihood of crystal formation increases exponentially with increasing urinary oxalate levels. Thus, factors that influence urinary oxalate production and excretion, including vitamin B6 (pyridoxine) and vitamin C (ascorbic acid), may alter the risk of stone formation.

The recommended daily allowance (RDA) for vitamin B6 is 2 mg/d. Oxalate production and excretion increases in the setting of vitamin B6 deficiency (1). In contrast, the administration of physiologic or pharmacologic doses of vitamin B6 (10 to 500 mg/d) decreased oxalate production in some kidney stone patients with mild hyperoxaluria (2–4). However, we found no significant association between vitamin B6 intake and risk of stone formation in our large prospective study in men, even for those consuming ≥40 mg/d (relative risk [RR] 0.91; 95% confidence interval [95% CI], 0.64 to 1.31) (5).

The RDA for vitamin C is 60 mg/d. Vitamin C can be metabolized to oxalate (6), which could increase oxalate excretion and hence the risk of calcium oxalate stone formation. Therefore, stone formers are frequently advised to avoid vitamin C supplements. However, short-term metabolic studies of urinary oxalate excretion after vitamin C loading have produced inconsistent results (7–9), perhaps due to less reliable oxalate measurements characteristic of older assays. The increase in urinary oxalate observed after experimental administration of high doses of vitamin C appears to be due to *in vitro* conversion of ascorbate to oxalate during the analytical procedure rather than *in vivo* conversion (7).

A large cross-sectional study in U.S. adults found that individuals who reported current vitamin C use were 10% less likely to report a history of kidney stone disease (10). However, the authors inquired about vitamin C intake after the kidney stone event; thus, the observed inverse association may have resulted from advice given to stone patients to avoid vitamin C supplements. In addition, that study did not adjust for other important dietary factors. We found no association between vitamin C intake and risk of stone formation in a prospective study in men (5).

Although women form stones at a rate one-third that of men, the reasons for the large differences are not completely understood. To clarify the association between the intake of vitamins B6 and C and the incidence of kidney stones in women, we studied this relation prospectively in a cohort of 85,557 women with no history of kidney stones.

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Materials and Methods

Study Population

In 1976, 121,701 female registered nurses between the ages of 30 and 55 yr residing in one of 11 U.S. states completed and returned the initial questionnaire and constitute the Nurses' Health Study (NHS) cohort (11). The cohort is followed by means of biennial mailed questionnaires that inquire about lifestyle practices and other exposures of interest, as well as the incidence of newly diagnosed disease. The population for the current analysis was limited to the women who answered the 1992 or the 1994 questionnaires, which inquired about a history of kidney stone disease, and who had completed at least one dietary questionnaire since dietary information was first collected in 1980.

We considered only cases that occurred during the 14-yr period between the return of the 1980 questionnaire and May 31, 1994. After we excluded women for whom the date of diagnosis could not be confirmed or fell outside the study period ($n = 3233$), 85,557 women with no history of kidney stones before the 1980 questionnaire remained in the study group.

Assessment of Diet

Participants were asked in 1980, 1984, 1986, and 1990 to complete semiquantitative food-frequency questionnaires on which they reported the average use of specified foods and beverages during the past year. The 1980 dietary questionnaire contained a list of 61 items, and the subsequent questionnaires contained approximately 130 items. Nutrient intake was computed from the reported frequency of consumption of each specified unit of food or beverage and from published data on the nutrient content of the specified portions (12,13). Beginning in 1980, information also was collected on supplemental vitamins, including vitamin C, either alone or as part of multivitamin preparations; a separate question on supplemental vitamin B6 intake was added starting in 1984. The multiple choice categories for supplemental vitamin C were (in mg/d): 0, 1 to 399, 400 to 700, 750 to 1250, and 1300 or more. Categories for supplemental vitamin B6 were (in mg/d): 0, 1 to 10, 10 to 39, 40 to 79, and 80 or more. The amounts of vitamins B6 and C in multivitamin preparations were determined by the brand, type, and frequency of reported use. The reproducibility and validity of the questionnaires in this cohort have been documented previously (12,13). The Pearson correlation coefficients for energy-adjusted vitamins B6 and C intake between the dietary records and the questionnaire were 0.54 and 0.73, respectively (12). After adjustment for the week-to-week variation of intake of vitamins B6 and C, the correlation coefficients were 0.58 and 0.75, respectively. After the exclusion of supplemental vitamin use, the correlation coefficients for vitamin B6 (0.54) and C (0.66) were slightly attenuated.

Nutrient values were adjusted for total energy intake using a regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable (13,14). Because total energy intake for a given person tends to be fixed within a narrow range, variations in nutrient intake are attributable largely to changes in composition of the diet, not the total amount of food consumed. Energy-adjusted values reflect the nutrient composition of the diet independent of the total amount of food consumed. In addition, energy adjustment reduces variation introduced by underreporting or overreporting of intake on the food-frequency questionnaire, thus improving the accuracy of nutrient measurements (13,14).

Assessment of Nondietary Factors

Body mass index (kg/m^2) was calculated based on information on height which was provided in 1976 and weight that was provided on each subsequent follow-up questionnaire.

Follow-Up and Ascertainment of Cases

On the 1992 biennial questionnaire, women were asked whether they had ever been diagnosed with a kidney stone. On the 1994 questionnaire, they were asked about a new diagnosis of a kidney stone since 1992. If a kidney stone was reported to have occurred after the return of the 1980 questionnaire (when dietary information was first collected), we mailed the subject a supplementary questionnaire to confirm the diagnosis and to ascertain the date of first occurrence, symptoms, other relevant medical conditions and the type of stone if known. The response rate to the supplementary questionnaire was 92 percent. The validity of the subjects' reports was evaluated by review of the medical records from a random sample of 90 of the women who reported a kidney stone. The records confirmed the diagnosis in all but one of the cases.

Statistical Analyses

The study design was prospective with the dietary information collected before the onset of the kidney stone symptoms. For each participant, person-months of follow-up were counted from the date of the return of the 1980 questionnaire to the date of a kidney stone, death, or May 31, 1994, whichever occurred first. Information on exposures of interest from the 1980 questionnaire was updated in 1984, 1986, and 1990. We allocated person-months of follow-up according to exposure status (*e.g.*, the category of vitamin use) at the start of each follow-up period. If information on vitamin intake was missing at the start of a time period, the subject was excluded from that time period. Subjects who reported a kidney stone on the biennial questionnaire but did not respond to the supplementary questionnaire were considered noncases in the analysis.

The relative risk—the incidence among women in a particular category of exposure divided by the corresponding rate in the comparison category—was used as the measure of association (15). Age-adjusted relative risks were calculated after stratification according to 5-yr age categories (15). The Mantel extension test was used to evaluate linear trends across categories of intake (16). We used a proportional hazards model to adjust for multiple risk factors simultaneously (17). The variables from the 1980 questionnaire in the proportional hazards model were updated in 1984, 1986, and 1990. The variables considered in these models were: vitamin B6 (five categories), vitamin C (five categories), age (in 5-yr categories), body mass index (seven categories), supplemental calcium (four categories), alcohol (six categories), and dietary intake of calcium, animal protein, potassium, sodium, sucrose, and total fluid (quintile groups). We selected these dietary variables based on our previous study, which demonstrated that these other dietary variables are related to risk of kidney stones (18). For all relative risks, we calculated 95% CI. All *P* values are two-tailed.

Results

Among 85,557 NHS women with no history of kidney stones before 1980, we confirmed 1078 incident cases during 980,308 person-years of follow-up from 1980 to 1994.

Vitamin B6

The characteristics of the cohort according to categories of energy-adjusted dietary vitamin B6 intake in 1986 are shown in

Table 1. The 1986 values were selected to demonstrate quantitatively the boundaries of the categories and are representative of the ranges of intake during the different time periods for the cohort. However, for the analyses, the actual values as calculated from the food-frequency questionnaire were used for each respective time period. In 1986, 9.0% of the women reported consuming 10 mg or more each day of vitamin B6. Because the amount of dietary vitamin B6 intake did not differ substantially among the categories, it was the intake of supplemental vitamin B6 that resulted in assignment to higher categories. Mean daily intake of potassium, magnesium, supplemental calcium, and vitamin C increased with increasing intake of vitamin B6 (Table 1).

After adjusting for age only, there was no significant association between the risk of stone formation and vitamin B6 intake. However, after also adjusting for the intake of other dietary factors, women in the highest vitamin B6 category had a significantly lower risk of stone formation. The relative risk of stone formation in women in the highest (≥40 mg/d) category of vitamin B6 intake compared with the lowest category (<3 mg/d) was 0.66 (95% CI, 0.44 to 0.98) (Table 2). The results did not change when the raw vitamin B6 values were used instead of the energy-adjusted vitamin values. We also compared the risk for those women consuming ≥100 mg/d and found that the relative risk (RR 0.59; 95% CI, 0.32 to 1.08) was not significantly different from those taking 40 to 99 mg/d (RR 0.71; 95% CI, 0.43 to 1.17).

Vitamin C

In 1986, 7.9% of the cohort reported consuming 1000 mg or more each day of vitamin C. Similar to vitamin B6, the amount of dietary vitamin C did not differ substantially among the categories of intake; thus, the use of vitamin C supplements resulted in assignment to the higher categories. Mean daily intake of potassium, magnesium, supplemental calcium, and vitamin B6 increased with increasing intake of vitamin C (Table 3).

After adjusting for age, there was no significant association between the risk of stone formation and vitamin C intake (Table 4). The relative risk of stone formation for women in the highest category (≥1500 mg/d) of vitamin C intake compared with the lowest (<250 g/d) was 0.98 (95% CI, 0.65 to 1.47). There was no material change in these results after controlling for dietary factors or when the raw vitamin C values were used instead of the energy-adjusted vitamin values. In a multivariate model that included vitamin C as a continuous variable, for every 500 mg of vitamin C consumed daily, the relative risk of stone formation was 1.03 (95% CI, 0.95 to 1.11).

Discussion

Our findings support the hypothesis that high doses of vitamin B6 reduce the risk of kidney stone formation in women. In addition, these prospective data do not support the belief that the risk of stone formation rises with increasing intake of vitamin C.

Vitamin B6

There are no randomized trials examining the impact of vitamin B6 supplementation on the risk of kidney stone formation. In uncontrolled studies, doses of 10 to 500 mg/d of pyridoxine were reported to decrease urinary oxalate (2–4) or stone recurrence rates (4,19) in calcium oxalate stone formers.

Table 1. Characteristics of 64,190 women according to category of energy-adjusted vitamin B6 intake in 1986 (the Nurses' Health Study)[a]

Characteristic	Vitamin B6 Category (mg/d)				
	<3 (n = 46,312)	3 to 4 (n = 4640)	5 to 9 (n = 7492)	10 to 39 (n = 2474)	40+ (n = 3272)
Age (yr)	52.3	54.0	53.6	53.3	52.1
Daily intake, mean					
vitamin B6, dietary (mg)	1.8	2.0	1.9	1.9	1.9
vitamin B6, supplemental (mg)	0.3	2.4	4.7	19.2	102.3
dietary calcium (mg)	711	751	742	746	737
supplemental calcium (mg)	286	505	525	575	655
animal protein (gm)	54	57	56	56	56
sodium (mg)	2873	2818	2798	2761	2757
potassium (mg)	3003	3234	3192	3249	3267
sucrose (gm)	37	36	36	36	36
magnesium (mg)	286	338	337	343	338
vitamin C (mg)	239	437	600	801	855
alcohol (gm)	6	6	6	6	6
caffeine (mg)	291	258	260	268	254
fluid (ml)	1993	2071	2062	2036	2038

[a] All values are means, standardized according to the age distribution of the entire cohort. Nutrient values (except for alcohol and total fluid) were adjusted for energy intake.

Table 2. Relative risk of symptomatic kidney stones, according to category of energy-adjusted vitamin B6 intake among 85,574 women (the Nurses' Health Study)

Parameter	Vitamin B6 Category (mg/d)					χ (P for trend)
	<3	3 to 4	5 to 9	10 to 39	40+	
No. of cases	836	78	100	36	28	
No. of person-years	760,913	67,765	91,411	26,390	33,829	
Age-adjusted relative risk	1.00	1.04	0.99	1.23	0.75	−0.44 (0.66)
95% CI	Referent	0.83 to 1.32	0.80 to 1.22	0.89 to 1.73	0.52 to 1.09	
Multivariate relative risk[b]	1.00	1.05	1.00	1.14	0.66	−2.08 (0.04)
95% CI[a]	Referent	0.88 to 1.24	0.79 to 1.26	0.79 to 1.64	0.44 to 0.98	

[a] CI, confidence interval.
[b] The multivariate model included age (in 5-yr age categories), body mass index (seven categories), alcohol (six categories), vitamin C (five categories), supplemental calcium (four categories), and dietary intake of calcium, animal protein, sodium, potassium, sucrose, caffeine, and total fluid (quintile groups).

Table 3. Characteristics of 64,190 women according to category of energy-adjusted vitamin C intake in 1986 (the Nurses' Health Study)[a]

Characteristic	Vitamin C Category (mg/d)				
	<250 (n = 39,242)	250 to 499 (n = 12,312)	500 to 999 (n = 7597)	1000 to 1499 (n = 3503)	1500+ (n = 1536)
Age (yr)	52.1	53.2	53.6	53.7	53.9
Daily intake, mean	148	337	700	1221	1833
vitamin C, dietary (mg)	131	195	166	165	176
vitamin C, supplemental (mg)	18	141	535	1055	1657
dietary calcium (mg)	710	734	736	741	743
supplemental calcium (mg)	270	401	521	665	802
animal protein (gm)	55	55	55	56	55
sodium (mg)	2909	2765	2768	2730	2708
potassium (mg)	2910	3274	3172	3242	3385
sucrose (gm)	36	37	37	36	37
magnesium (mg)	285	322	321	333	356
vitamin B6 (mg)	4	9	18	27	50
alcohol (gm)	6	6	7	6	5
caffeine (mg)	298	254	261	263	270
fluid (ml)	1957	2126	2086	2092	1949

[a] All values are means, standardized according to the age distribution of the entire cohort. Nutrient values (except for alcohol and total fluid) were adjusted for energy intake.

In contrast, investigators who prescribed 200 mg daily found no increase in urinary oxalate among stone formers but found a surprisingly significant 21% increase in urine oxalate among healthy subjects (20). In our observational study in men, we found no beneficial effect of vitamin B6 on the risk of incident stone formation, even for intakes 40 mg/d and higher (RR 0.91; 95% CI, 0.64 to 1.31) (5). The reason for the difference in results between men and women is unclear. We are unaware of any data that suggest oxalate metabolic pathways differ by gender.

Vitamin C

Short-term studies of the effect of large doses of oral vitamin C on urinary oxalate excretion have produced conflicting results (7–9). In one study of 39 healthy volunteers, urinary oxalate increased by 50% in subjects who received 1000 mg of vitamin C daily; no further increase was observed in those taking 9000 mg daily (9). Another study of 15 patients, who had recently undergone extracorporeal lithotripsy, found a 39% increase in urinary oxalate among those who received 1000 mg daily and a 100% increase with 2000 mg daily (8).

To determine whether the variability of results in previous studies was due to analytical errors, urinary oxalate levels were measured using modified ion chromatography after the oral administration of 1 to 10 g of vitamin C to healthy adults (7). Vitamin C added directly to urine resulted in a statistically significant but modest increase in measured oxalate, demonstrating that vitamin C was converted to oxalate during anal-

Table 4. Relative risk of symptomatic kidney stones, according to category of energy-adjusted vitamin C intake among 85,557 women (the Nurses' Health Study)

Parameter	Vitamin C Category (mg/d)					χ (P for trend)
	<250	250 to 499	500 to 999	1000 to 1499	1500+	
No. of cases	739	150	121	44	24	
No. of person-years	659,783	152,494	102,770	43,503	21,758	
Age-adjusted relative risk	1.00	0.87	1.05	0.90	0.98	−0.46 (0.64)
95% CI	Referent	0.73 to 1.04	0.87 to 1.27	0.67 to 1.22	0.65 to 1.47	
Multivariate relative risk[a]	1.00	0.89	1.08	0.95	1.06	0.79 (0.43)
95% CI	Referent	0.74 to 1.08	0.87 to 1.34	0.69 to 1.31	0.69 to 1.63	

[a] The multivariate model included age (in 5-yr age categories), body mass index (seven categories), alcohol (six categories), vitamin B6 (five categories), supplemental calcium (four categories), and dietary intake of calcium, animal protein, sodium, potassium, sucrose, caffeine, and total fluid (quintile groups).

ysis. Thus, the increase in urine oxalate values that followed the ingestion of varying doses of vitamin C could be entirely accounted for by the conversion of vitamin C to oxalate during the analytical procedure. Therefore, the authors concluded that there was no true increase in urinary oxalate, despite the greatly increased vitamin C intake.

The results from studies that examined the association between vitamin C and risk of stone formation, and not only changes in urinary oxalate excretion, have not demonstrated an increase in risk. Case-control studies of the association between vitamin C intake and kidney stones found similar (21,22) or decreased (23,24) intake among the cases. A large cross-sectional study found that women currently consuming vitamin C supplements had a 10% *lower* risk of a self-reported history of kidney stones (10). However, since this was a cross-sectional rather than prospective study, this inverse association may be attributed to the discontinuation of vitamin C supplements by stone formers in response to medical advice. In our prospective observational study in men, we found no increased risk of incident stone formation, even for intakes of vitamin C ≥1500 mg/d (RR 0.78; 95% CI, 0.54 to 1.11) (5).

We avoided biased recall of diet by collecting vitamin intake data before the diagnosis of kidney stones. In addition, we adjusted for other dietary and nondietary risk factors for stone formation. Although we did not have information on the type of stone, we believe that more than 80% of the stones in our cohort were calcium oxalate (25). Because of the beneficial effects of large doses of pyridoxine on reducing oxalate excretion in patients with primary hyperoxaluria (26), it remains possible that a higher intake of vitamin B6 may have a positive effect in a subset of kidney stone patients with marked hyperoxaluria. However, we did not have sufficient information on urinary oxalate excretion to evaluate this issue.

The validity of our dietary questionnaire has been carefully documented, yet we recognize that in our study vitamin intake was not perfectly measured. Nevertheless, our findings of an inverse association with vitamin B6 cannot be explained by random misclassification. Moreover, most of the vitamin consumption in the high categories was from supplements that are well reported in this cohort. The range of intake of vitamin C was substantial, and the mean daily consumption in the highest category was more than 30 times greater than the U.S. recommended dietary allowance of 60 mg. Therefore, the lack of an association with vitamin C was not due to insufficient variation or magnitude of intake.

These results are generalizable to women, 34 yr of age or older, who have no history of kidney stones. In addition, given that the pathophysiology of stone formation is the same for both incident and recurrent kidney stones, it is likely that our results also apply to women who have a history of calcium oxalate stones. The results of this study of women and vitamin C intake are consistent with our previous findings in men. However, the inverse association between vitamin B6 intake and stone formation in women was not observed in men (5).

Large doses of vitamin B6 and C are taken relatively frequently by adults in the United States and may be beneficial for a variety of clinical conditions. Our results suggest that ≥40 mg/d of vitamin B6 intake may reduce the risk of stone formation in women. However, our findings for vitamin C, which have been consistent for women and men, do not support the practice of routine restriction of vitamin C to prevent kidney stones.

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