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Vitamin B6 Intake and the Risk of Incident Kidney Stones

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Abstract

Background—Higher vitamin B6 intake might reduce urinary excretion of oxalate, one of the major determinants of risk for calcium oxalate kidney stones. Previous studies investigating the association between intake of vitamin B6 and risk of stones found conflicting results.

Objective—We sought to investigate the association in three large prospective cohorts.

Methods—We prospectively examined the association in the Health Professionals Follow-up Study (HPFS; n = 42,919 men), Nurses' Health Study I (NHS I; n = 60,003 older women), and Nurses' Health Study II (NHS II; n = 90,629 younger women). Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident stones across categories of total vitamin B6 intake (<3.0, 3.0–4.9, 5.0–9.9, 10.0–39.9, 40.0 mg/day) were generated with Cox proportional hazards regression models adjusted for potential confounders.

Results—During 3,316,846 person-years of follow-up, 6,576 incident kidney stones were confirmed. In univariate and multivariate analyses, there was no association between intake of vitamin B6 and incident stones. The HR for stones in the highest category compared with the lowest was 1.05 (95% CI 0.85, 1.30; p-value for trend = 0.61) for HPFS, 0.95 (95% CI 0.76, 1.18; p-value for trend = 0.42) for NHS I, and 1.06 (95% CI 0.91, 1.24; p-value for trend = 0.34) for

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Statement of authors' contributions to manuscript

PMF, ENT, GG and GCC designed research; PMF, ENT and GCC conducted research; PMF analyzed data; PMF, ENT, GG and GCC wrote the paper; PMF and GCC had primary responsibility for final content. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest: GCC: Consultant: Allena Pharmaceuticals, AstraZeneca, Exponent; Royalties: UpToDate (author and Section Editor); Honorarium: American Society of Nephrology (Editor-in-Chief, Clinical Journal of the American Society of Nephrology). All other authors have nothing to disclose

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

NHS II. The pooled adjusted HR for the highest category compared with the lowest was 1.03 (95% CI 0.92, 1.15; p-value for trend = 0.60).

Conclusions—Intake of vitamin B6 is not associated with risk of incident kidney stones.

Introduction

Vitamin B6 (pyridoxine) intake might lower the urinary excretion of oxalate, which in turn is one of the major determinants of calcium oxalate kidney stones.(1) The transamination of glyoxylate to glycine requires vitamin B6 as a cofactor of the enzyme alanine-glyoxylate aminotransferase and a deficiency of vitamin B6 could increase the amount of glyoxylate transformed into oxalate by the lactate dehydrogenase. It has been reported that vitamin B6 deficiency results in increased production and excretion of oxalate,(2) and supplementation of vitamin B6 has been shown to reduce urinary excretion of oxalate in some studies(3–7) but not in others.(8,9) Previous cohort studies investigating the association between intake of vitamin B6 and incident kidney stones found conflicting results, with no association among males participating in the Health Professionals Follow-up Study (HPFS)(10) and an inverse association among older females in the Nurses' Health Study (NHS) I.(11) We sought to investigate the association between intake of vitamin B6 and incident kidney stones in the same cohorts after additional follow-up time, as well as in an additional cohort of younger females in the NHS II in which the association was not investigated before.

Methods

Study populations

The HPFS was established in 1986 with the enrollment of 51,529 male health professionals aged between 40 and 75 years; the NHS I was established in 1976 with the enrollment of 121,700 female nurses aged between 30 and 55 years; the NHS II was established in 1989 with the enrollment of 116,430 female nurses aged between 25 and 42 years. At enrollment, participants from each cohort completed a questionnaire with detailed information on lifestyle, medical history, and medications. Participants subsequently were followed with biennial questionnaires including updated information and newly diagnosed diseases. These studies were approved by the Partners HealthCare institutional review board.

For the current analysis, follow-up was started in 1986 for HPFS and NHS I and 1991 for NHS II (the dates of the first detailed food-frequency questionnaire [FFQ]) and went through January 2012 for HPFS, May 2012 for NHS I and May 2011 for NHS II. We only included participants without a history of kidney stones at baseline; furthermore, participants with a history of malignancy (except for non-melanoma skin cancer) at baseline were excluded and those who developed malignancies during follow-up were censored. For NHS I, only participants who answered questionnaires in 1992 (the year of the first lifetime kidney stone history inquiry) or later were included.

Assessment of vitamin B6 and other nutrients

In 1986 (HPFS, NHS I) and 1991 (NHS II), participants completed a FFQ asking about the average annual intake of more than 130 foods and 22 beverages; subsequently, the

information was updated through FFQs every four years. Frequencies of consumption of each unit of food were used to compute intakes of nutrients using data from the United States Department of Agriculture, except for oxalate content which was measured by capillary electrophoresis in the majority of foods from the FFQ.(12,13) The FFQ also contains information on multivitamin and vitamin B6 supplements, inquiring about the specific brand and the amount and frequency of use, used to calculate the amount of vitamin B6 as the frequency of intake multiplied by composition. For the current analysis, we looked at intakes of total vitamin B6, i.e. the sum of vitamin B6 from diet and supplements. All nutrients were energy-adjusted to account for total amount of food eaten. FFQs were previously found to be reproducible and valid in HPFS and NHS I.(14,15)

Assessment of kidney stones

Participants who reported the occurrence of a kidney stone on the biennial questionnaire were asked to complete a supplementary questionnaire to establish the date of occurrence and accompanying symptoms. For this analysis, only kidney stones accompanied by pain and/or hematuria were considered. Evaluation of medical records among 582 participants from HPFS, 194 from NHS I and 858 from NHS II who reported a kidney stone confirmed the diagnosis in 95%, 96% and 98% of cases, respectively. Stone composition, available for a subgroup of cases, was 50% calcium oxalate in 77% of NHS I, 79% of NHS II, and 86% of HPFS participants.(16)

Assessment of other covariates

Information on age, BMI, history of diabetes, history of hypertension, use of thiazides and amount of calcium supplements was obtained from the biennial questionnaire. Self-reported weight, used to calculate BMI, was validated in the HPFS and NHS I cohorts.(17)

Statistical analysis

The analysis of incident stone formation was prospective; dietary intakes were assessed before the diagnosis of the incident kidney stone. For each cohort, participants were divided into categories of total vitamin B6 intake (<3.0, 3.0–4.9, 5.0–9.9, 10.0–39.9, 40.0 mg/day); time at risk was calculated as time from start of follow-up to either an incident kidney stone, loss to follow-up, death or censoring (whichever happened first). Cox proportional hazards regression models generated hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for age (continuous), BMI (13 categories), history of diabetes (yes vs no), history of hypertension (yes vs no), use of thiazides (yes vs no), supplemental calcium intake (4 categories) and dietary intakes of fluid, calcium, sodium, potassium, animal protein, fructose, oxalate, vitamin C, caffeine, magnesium (all quintiles), and alcohol (4 categories). Information on vitamin B6 intakes and other covariates were updated every 4 years. Tests for linear trends were constructed by analyzing the mid-point value for each category as a continuous variable. To investigate the association between extreme intakes of total vitamin B6 and stones, we also repeated the analyses after further dividing the <3.0 mg/day category into <1.5, 1.5–1.9, 2.0–2.4, 2.5–2.9 mg/day categories and the 40.0 mg/day category into 40.0–69.0 and 70.0 mg/day categories. Effect modification by age (<50 vs ≥50 years), BMI (<25 vs ≥25 kg/m²) and dietary oxalate intake (below or above the cohort-specific median) was investigated through interaction terms. For each analysis, we evaluated between-cohort

heterogeneity; pooled estimates obtained by random-effects meta-analysis are presented because the p-value for heterogeneity was >0.05 .

Results

A total of 193,676 participants were included in the analysis of incident kidney stones (42,919 from HPFS, 60,128 from NHS I and 90,629 from NHS II). Baseline characteristics of the study participants in the lowest and highest categories of vitamin B6 intake are shown in Table 1. The amount of calcium from supplements and total intakes of potassium, oxalate, magnesium and total vitamin C tended to be higher in the highest compared with the lowest categories of vitamin B6 in all cohorts. Overall, 6,308 incident kidney stones were confirmed during 3,108,264 person-years of follow-up.

Estimates of association between categories of vitamin B6 and incident stones are reported in Table 2. In univariate analyses, there was no association between intake of vitamin B6 and incident stones. The HR for stones in the highest category compared with the lowest was 0.92 (95% CI 0.77, 1.10; p-value for trend = 0.81) for HPFS, 0.84 (95% CI 0.69, 1.02; p-value for trend = 0.16) for NHS I, and 0.93 (95% CI 0.81, 1.07; p-value for trend = 0.79) for NHS II. After multivariate adjustment, the results did not change significantly: the HR for stones in the highest category compared with the lowest was 1.05 (95% CI 0.85, 1.30; p-value for trend = 0.61) for HPFS, 0.95 (95% CI 0.76, 1.18; p-value for trend = 0.42) for NHS I, and 1.06 (95% CI 0.91, 1.24; p-value for trend = 0.34) for NHS II. The pooled adjusted HR for the highest category compared with the lowest was 1.03 (95% CI 0.92, 1.15; p-value for trend = 0.60). After finer stratification into 9 categories of intake, the results did not change substantially (pooled adjusted p-value for trend = 0.87).

There was no significant effect modification by age, BMI or dietary oxalate intake.

Discussion

Vitamin B6 is a water-soluble vitamin whose recommended daily allowance is 1.3 mg for males and females 19 to 50 years, 1.7 mg for males ≥ 50 years and 1.5 mg for females ≥ 50 years.(18) The typical amount of vitamin B6 in multivitamins is 1.5–5.0 mg. Vitamin B6 might reduce oxalate excretion by reducing its production in the liver. In fact, it is a cofactor of the alanine-glyoxylate aminotransferase, which metabolizes glyoxylate into glycine. When this metabolic pathway is limited by insufficient levels of pyridoxine, more glyoxylate would be available for conversion into oxalate by the lactate dehydrogenase. Even though a dose-response relationship between vitamin B6 and urine oxalate would be expected given the purported mechanism of action, previous studies did not consistently report such a dose-response relationship.

In our longitudinal prospective study, we found no association between intake of vitamin B6 and risk of kidney stones even among individuals with high vitamin B6 intake. Although to the best of our knowledge no randomized controlled studies are available on the effect of vitamin B6 on the risk of kidney stones, some studies have previously reported a beneficial effect of vitamin B6 in reducing urinary excretion of oxalate, a major determinant of calcium oxalate stone risk. For instance, Balcke and colleagues showed that administration

of vitamin B6 in 12 patients with calcium oxalate calculi resulted in a 30% reduction in urine oxalate.(3) Similarly, Mitwalli et al. reported a significant reduction in urine oxalate after administration of 250–500 mg of vitamin B6 in 12 patients with calcium oxalate calculi and hyperoxaluria.(5) A retrospective analysis of 95 stone formers with idiopathic hyperoxaluria showed that administration of up to 200 mg/day of vitamin B6 resulted in a 30% reduction of urine oxalate (from 58 to 41 mg/24h), with normalization of hyperoxaluria in 39% of patients.(7) However, other studies failed to show a beneficial effect of vitamin B6 supplementation: in a study conducted on 7 patients with idiopathic hyperoxaluria and 10 healthy controls, administration of 200 mg/day of pyridoxine had no effect on urine oxalate among the former, and resulted in a paradoxical increase in urine oxalate among the latter.(8) More recently, a comparatively larger study analyzed the effect of a 7-day course of vitamin B6 at a dose of 300 mg/day on urinary excretion of oxalate among 55 idiopathic calcium stone formers (40 with and 15 without hyperoxaluria) and 50 healthy subjects: urine oxalate did not change substantially in any group.(9) In the HPFS and NHS cohorts, intake of total vitamin B6 was not associated with urinary oxalate excretion.(19)

Our study confirms the previous findings of a lack of association between intake of vitamin B6 and risk of stones among males;(10) we did not confirm the previous inverse association among older females.(11) The reason for such discrepancy might be the increased power of the current study due to a longer follow-up time and larger number of incident events.

The strengths of our study include the analysis of data from three large, ongoing and well characterized cohorts with long follow-up time and validated and updated information on other nutrients and comorbidities. Our study also has limitations, including the fact that the majority of the participants were white and the lack of stone and urine composition data for all the participants; furthermore, the doses of vitamin B6 consumed by participants even in the highest categories were lower than those used in the previous interventional studies cited. Finally, our study does not exclude the possibility that vitamin B6 may be associated with lower risk in selected individuals. For example, some patients with type 1 primary hyperoxaluria would benefit from high dose vitamin B6 supplementation.(20,21)

In conclusion, intake of vitamin B6 is not associated with risk of incident kidney stones.

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Abbreviations

BMI	body mass index
CI	confidence interval

FFQ	food frequency questionnaire
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
NHS	Nurses' Health Study

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Table 1
Age-standardized baseline characteristics in the lowest and highest categories of vitamin B6 intake

	Categories of vitamin B6 intake (mg/day)					
	HPFS		NHS I		NHS II	
	<3.0 (n=24,411)	40.0 (n=1,917)	<3.0 (n=36,626)	40.0 (n=3,056)	<3.0 (n=53,244)	40.0 (n=3,748)
Vitamin B6 intake, mg/day	2.1(0.4)	105.7(57.5)	1.9(0.4)	103.8(54.0)	2.1(0.4)	112.1(60.6)
Age, years*	53(10)	55(10)	53(7)	52(7)	37(5)	38(4)
BMI, kg/mq	25.7(3.4)	25.2(3.1)	25.4(4.8)	24.9(4.6)	24.7(5.5)	24.0(4.9)
History of diabetes, %	3	3	3	3	1	1
History of hypertension, %	21	22	24	23	6	7
Thiazide use, %	9	9	13	14	2	3
Calcium supplements use, %	8	75	43	86	14	64
Alcohol intake, g/day	11.7(15.8)	11.2(15.5)	6.2(10.7)	5.9(10.5)	3.2(6.1)	3.4(6.7)
Dietary calcium, mg/day	786(303)	813(303)	707(250)	734(256)	853(296)	893(306)
Potassium, mg/day	3,295(623)	3,829(866)	2,987(584)	3,266(718)	2,848(516)	3,050(561)
Animal protein, g/day	66.9(16.7)	69.1(19.7)	54.2(13.4)	55.6(15.0)	63.2(15.9)	63.7(18.6)
Oxalate, mg/day	135(105)	171(140)	113(82)	136(116)	127(104)	158(141)
Magnesium, mg/day	328(62)	415(104)	282(56)	338(84)	291(57)	359(101)
Fructose, g/day	24.3(11.1)	27.6(12.3)	21.2(9.0)	22.9(9.7)	22.5(11.5)	23.9(11.0)
Vitamin C, mg/day	239(262)	1,277(647)	213(218)	852(588)	159(172)	680(645)
Caffeine, mg/day	260(259)	206(240)	297(231)	251(218)	257(227)	234(222)
Fluid volume, L/day	1.9(0.8)	1.9(0.8)	2.0(0.7)	2.0(0.7)	2.1(0.8)	2.1(0.8)

Values are means(SD) or percentages and are standardized to the age distribution of the study population.

* Value is not age-adjusted. BMI, body mass index; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study

Table 2

Relative risk of kidney stones by categories of total vitamin B6

	<3.0 mg/d	3.0–4.9 mg/d	5.0–9.9 mg/d	10.0–39.0 mg/d	40.0 mg/d	p-value for trend
HPFS						
Median (mg/d)	2.1	3.8	6.6	15.1	80.2	
Cases	998	454	296	74	141	
Person-years	305,863	167,129	114,732	29,644	52,120	
Age-adjusted HR	1.00 (Ref.)	0.88 (0.79, 0.99)	0.86 (0.75, 0.98)	0.79 (0.62, 1.00)	0.92 (0.77, 1.10)	0.81
MV-adjusted HR	1.00 (Ref.)	1.00 (0.88, 1.14)	1.02 (0.87, 1.20)	0.87 (0.67, 1.14)	1.05 (0.85, 1.30)	0.61
NHS I						
Median (mg/d)	1.8	3.8	6.3	21.2	80.1	
Cases	817	423	188	48	123	
Person-years	586,934	338,958	152,171	38,973	101,988	
Age-adjusted HR	1.00 (Ref.)	0.92 (0.82, 1.04)	0.93 (0.79, 1.10)	0.89 (0.66, 1.19)	0.84 (0.69, 1.02)	0.16
MV-adjusted HR	1.00 (Ref.)	1.04 (0.90, 1.19)	1.07 (0.88, 1.28)	1.02 (0.75, 1.39)	0.95 (0.76, 1.18)	0.42
NHS II						
Median (mg/d)	2.0	3.8	6.4	13.7	94.5	
Cases	1,617	719	295	138	245	
Person-years	735,699	372,746	141,022	62,457	116,412	
Age-adjusted HR	1.00 (Ref.)	0.86 (0.78, 0.94)	0.93 (0.82, 1.05)	0.98 (0.83, 1.17)	0.93 (0.81, 1.07)	0.79
MV-adjusted HR	1.00 (Ref.)	0.94 (0.84, 1.04)	1.04 (0.89, 1.20)	1.11 (0.91, 1.35)	1.06 (0.91, 1.24)	0.34
Pooled						
Age-adjusted HR	1.00 (Ref.)	0.88 (0.83, 0.93)	0.90 (0.83, 0.98)	0.89 (0.78, 1.01)	0.91 (0.82, 1.00)	0.31
MV-adjusted HR	1.00 (Ref.)	0.98 (0.91, 1.05)	1.04 (0.94, 1.14)	1.00 (0.87, 1.15)	1.03 (0.92, 1.15)	0.60

MV model adjusted for age, BMI, history of diabetes, history of hypertension, use of thiazides, supplemental calcium intake and intakes of fluid, calcium, sodium, potassium, animal protein, fructose, oxalate, vitamin C, caffeine, magnesium and alcohol. For illustrative purposes, medians refer to the first time period.