AJKD
Original Investigation

Total, Dietary, and Supplemental Vitamin C Intake and Risk of Incident Kidney Stones

Pietro Manuel Ferraro, MD, MSc,[1,2] Gary C. Curhan, MD, ScD,[2] Giovanni Gambaro, MD, PhD,[1] and Eric N. Taylor, MD, MSc[2,3]

Background: Previous studies of vitamin C and kidney stones were conducted mostly in men and either reported disparate results for supplemental and dietary vitamin C or did not examine dietary vitamin C.

Study Design: Prospective cohort analysis.

Setting & Participants: 156,735 women in the Nurses' Health Study (NHS) I and II and 40,536 men in the Health Professionals Follow-up Study (HPFS).

Predictor: Total, dietary, and supplemental vitamin C intake, adjusted for age, body mass index, thiazide use, and dietary factors.

Outcomes: Incident kidney stones.

Results: During a median follow-up of 11.3 to 11.7 years, 6,245 incident kidney stones were identified. After multivariable adjustment, total vitamin C intake (<90 [reference], 90-249, 250-499, 500-999, and ≥1,000 mg/d) was not significantly associated with risk for kidney stones among women, but was among men (HRs of 1.00 [reference], 1.19 [95% CI, 0.99-1.46], 1.15 [95% CI, 0.93-1.42], 1.29 [95% CI, 1.04-1.60], and 1.43 [95% CI, 1.15-1.79], respectively; *P* for trend = 0.005). Median total vitamin C intake for the 500- to 999-mg/d category was ~700 mg/d. Supplemental vitamin C intake (no use [reference], <500, 500-999, and ≥1,000 mg/d) was not significantly associated with risk for kidney stones among women, but was among men (HR, 1.19 [95% CI, 1.01-1.40] for ≥1,000 mg/d; *P* for trend = 0.001). Dietary vitamin C intake was not associated with stones among men or women, although few participants had dietary intakes > 700 mg/d.

Limitations: Nutrient intakes derived from food-frequency questionnaires, lack of data on stone composition for all cases.

Conclusions: Total and supplemental vitamin C intake was significantly associated with higher risk for incident kidney stones in men, but not in women.

Am J Kidney Dis. 67(3):400-407.

INDEX WORDS: Kidney disease; nutrition; diet; supplements; urolithiasis; vitamin C; ascorbic acid; kidney stone formation; incident kidney stone; calcium oxalate; urinary oxalate excretion; food-frequency questionnaire (FFQ); gender difference; risk factor.

Kidney stones are common, with a lifetime prevalence of ~10% in the US population. Diet is thought to play an important role in the development of kidney stones, particularly intakes of calcium,[1-3] sodium,[1,3] fructose,[4] water, and other beverages.[5-8] Ascorbic acid, or vitamin C, is an essential nutrient acting as a cofactor in several enzymatic pathways, the main dietary sources of which are fresh fruits and vegetables. Ingested vitamin C is partly converted to oxalate and excreted in urine, thus potentially increasing the risk for calcium oxalate stone formation.[9,10] In a metabolic study of 24 individuals, 2 g/d of ascorbic acid increased urinary oxalate excretion by ~22%.[11]

Two previous epidemiologic studies have addressed kidney stone risk associated with vitamin C intake in men. In a prospective cohort study of men in the Health Professionals Follow-up Study (HPFS), ≥1,000 mg/d of total vitamin C intake was associated with a 41% higher risk for stones compared with ≤90 mg/d after adjusting for age, body mass index (BMI), use of thiazide diuretics, and dietary factors.[12] Recently, another study also reported a positive association between supplemental vitamin C intake and kidney stones in a cohort of 23,355 Swedish men; the multivariable-adjusted relative risk associated with supplemental vitamin C use was almost double compared to no use.[13] To date, the only study in women was performed in the Nurses' Health Study (NHS) I cohort and found no association between vitamin C intake and risk for stones.[14]

From the [1]Division of Nephrology, Department of Medical Sciences, Columbus-Gemelli University Hospital, Catholic University of the Sacred Heart, Rome, Italy; [2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and [3]Division of Nephrology and Transplantation, Maine Medical Center, Portland, ME.

Received June 4, 2015. Accepted in revised form September 1, 2015. Originally published online October 10, 2015.

Address correspondence to Pietro Manuel Ferraro, MD, MSc, Division of Nephrology–Renal Program, Department of Medical Sciences, Columbus-Gemelli University Hospital, Catholic University of the Sacred Heart, 00168, Rome, Italy. E-mail: manuel.ferraro@channing.harvard.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.09.005

However, the relationship between vitamin C intake and kidney stone formation remains unclear. First, the different results for men and women warrant further investigation. Dietary risk factors for kidney stones may vary by sex.[3,12,15] Second, the risk associated with higher intake (≥1,000 mg/d) of supplemental vitamin C in the previous study in HPFS was of borderline statistical significance (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.97-1.39; P for trend = 0.01).[12] Finally, interpretation of urinary oxalate excretion rates after vitamin C loading in metabolic studies may be complicated by ex vivo nonenzymatic conversion of urinary vitamin C into oxalate.[16]

To examine the independent associations of total, supplemental, and dietary vitamin C intake and risk for kidney stones in women, we analyzed data from a large prospective cohort, the NHS II. We also updated our previous analyses of the NHS I and HPFS cohorts to include 12 years of additional follow-up for each cohort, which provided greater statistical power.

METHODS

Study Population

The NHS I enrolled 121,700 female nurses aged 30 to 55 years in 1976, NHS II enrolled 116,430 female nurses aged 25 to 42 years in 1989, and HPFS enrolled 51,529 male health professionals aged 40 to 75 years in 1986. Participants were asked to complete biennial questionnaires with information on medical history, lifestyle, and medications. Information from the questionnaires was updated every 2 years, or every 4 years for the food-frequency questionnaires (FFQs). For the current analysis, participants who reported a history of kidney stones prior to the start of time at risk were excluded from the analysis. Similarly, those with a history of cancer (except for nonmelanoma skin cancer) prior to baseline were excluded from the analysis, and those who developed cancer during follow-up were censored because this condition might have affected their dietary or other behaviors. These studies were approved by the Partners HealthCare Institutional Review Board. Return of completed baseline and biennial questionnaires was accepted by the institutional review board as implied informed consent.

Assessment of Vitamin C and Other Nutrient Intake

In 1986 (NHS I and HPFS) and 1991 (NHS II), participants were asked to complete an FFQ that asked about the average use of more than 130 foods and 22 beverages in the previous year. Dietary information was updated every 4 years. Validation studies have demonstrated the reliability of the FFQ.[17,18] Intake of dietary factors was calculated from the reported frequency of consumption of each specified unit of food and, except for oxalate, from US 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 of frequently consumed foods written in, was measured by capillary electrophoresis as previously described.[19] The FFQ also inquires about vitamin and mineral supplements. Users of multivitamins and vitamin C supplements are asked to name the specific brand and provide the amount and frequency of use. Our database contains the composition of more than 1,000 brands of multivitamins and calculates the amount of vitamin C (and other vitamins and minerals) as the frequency of intake multiplied by composition. The same method is used for individual vitamin C supplements. For the current analysis, we used data from the FFQ for total vitamin C (dietary plus supplement sources) intake; alcohol intake; dietary intake of calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, and total fluids; and calcium supplements. All nutrients were energy-adjusted.

Assessment of Kidney Stones

Participants who reported an incident kidney stone were asked to complete a supplementary questionnaire about the date of occurrence and associated signs and symptoms, such as pain or hematuria. A kidney stone associated with pain or hematuria was the study outcome. Medical record validation studies confirmed the kidney stone diagnosis in >95% of cases among participants who submitted the supplementary questionnaire.[20] Stone composition was available for a subsample of cases and was found to be ≥50% calcium oxalate in 77% of NHS I, 79% of NHS II, and 86% of HPFS participants.[20]

Assessment of Other Covariates

Updated information from the questionnaires was used for the following variables: age, BMI, and thiazide diuretic use. Self-reported weight, from which BMI was calculated, was validated in the NHS I and HPFS cohorts.[21]

Statistical Analysis

The study design was prospective; information for diet was collected before the diagnosis of the kidney stone. We analyzed the association between total vitamin C intake and risk for stones using categories of vitamin C of <90, 90 to 249, 250 to 499, 500 to 999, and ≥1,000 mg/d. We selected these cutoff points based on our previous study in men.[12] We updated exposure and covariates every 4 years. We allocated person-time contributed by each participant during follow-up to the respective category of vitamin C intake and calculated incidence rates of kidney stones for each category. Age- and multivariable-adjusted HRs and 95% CIs for stones in each category of vitamin C intake were computed separately in each cohort with Cox proportional hazards regression models. We adjusted for age, BMI (13 categories), thiazide use (yes/no), supplemental calcium intake (no use, <100, 100-499, and ≥500 mg/d), alcohol intake (7 categories), and dietary intakes of calcium, sodium, potassium, magnesium, fructose, oxalate, phytate, animal protein, and fluid (all quintiles). We further analyzed the association using quintiles of total vitamin C intake and repeated the analyses in the NHS I and NHS II cohorts with a referent category of total vitamin C intake < 75 mg/d, which is the recommended daily allowance for women. Linear trends were evaluated using midpoints for categories of vitamin C intake and median values of vitamin C intake for quintiles; nonlinear relations were explored with models that included total vitamin C intake using restricted cubic splines with knots at quintiles. Finally, we constructed models of dietary and supplemental vitamin C intake separately with the following categories: <90, 90 to 249, and ≥250 mg/d for dietary intake; and no use, <500, 500 to 999, and ≥1,000 mg/d for supplemental intake. Also in these analyses, midpoints for each category were used to test for linear trends across categories. Time at risk was 1986 to 2006 for NHS I, 1991 to 2011 for NHS II, and 1986 to 2010 for HPFS.

Estimates obtained from the NHS I and NHS II cohorts were pooled with random-effects meta-analysis after evaluation of heterogeneity. Pooled results are presented for the 2 cohorts. For descriptive tables, variables were age-standardized using direct standardization to the overall age distribution (in 5-year age categories) in the study population.

RESULTS

The analysis included 197,271 participants with 2,494,789 person-years of follow-up. During a median