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Antibiotic Use and Risk of Incident Kidney Stones in Female Nurses

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Abstract

Rationale & Objective.—The intestinal microbiome may affect urinary stone disease (USD) by modulating the amount of oxalate absorbed from the intestine and subsequently excreted in the urine. This study sought to explore the association between antibiotics, which alter the intestinal microbiota, and the risk of USD.

Study design.—Prospective cohort study.

Setting & Participants.—5,010 women in the Nurses' Health Study (NHS) I and II who had collected 24-hour urine samples.

Exposures.—Use of antibiotics during the age range of 40-49 (NHS II), 40-59 (NHS I) and 20-39 years (both cohorts).

Outcomes.—Incident, symptomatic USD; urine composition.

Analytical approach.—Cause-specific hazards regression adjusted for age, BMI, comorbidities, thiazide use, and dietary factors. Follow-up was censored at the time of asymptomatic kidney stones, cancer, or death.

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Results.—Cumulative use of antibiotics for a total of 2 months or more during the age range of 40-49 years (NHS II) and 40-59 years (NHS II) was associated with a significantly higher risk of developing incident stones compared with no use (pooled HR 1.48; 95% CI, 1.12-1.96). Similar results were found for the period 20-39 years (pooled HR, 1.36; 95% CI, 1.00-1.84). Results remained unchanged after excluding participants who reported urinary tract infection with their stone event or as the most common reason for antibiotic use. Urine composition was generally similar across antibiotic groups except for marginally lower urine pH and citrate among those taking antibiotics for 2 months or more.

Limitations.—Observational design; lack of information on the type of antibiotic used; relatively large span of time between antibiotic use and urine collection.

Conclusions.—Use of antibiotics for >2 months in early adulthood and middle age is associated with higher risk of USD in later life.

Keywords

Antibiotics; Cohort studies; Urine chemistry; Urolithiasis; kidney stone; stone formation; intestinal microbiome; urine composition; cumulative antibiotic use; lithogenesis; women; antibacterial agents; drug effects; bacterial infection

Introduction

Kidney stones are increasingly common, with an estimated prevalence in the most recent NHANES survey of about 9%.[1] The intestinal microbiome may play a role in the development of kidney stones by influencing the metabolism of substances involved in stone formation. For example, the normal intestinal microbiome hosts *Oxalobacter formigenes,* a specialist oxalotrophe that degrades oxalate in the intestine, thus reducing its absorption and subsequently its urinary excretion; it is also thought to stimulate intestinal secretion of oxalate.[2] More generally, recent studies suggest that the intestinal microbiome of individuals affected with kidney stones might be different than those without a history of stones.[3,4]

Antibiotics are frequently used in the general population and have the potential to modify the intestinal microbiome. Given the purported role of intestinal bacteria in the development of kidney stones, it could be hypothesized that the prolonged use of antibiotics could increase the risk of forming stones; furthermore, it could also be speculated that antibiotics could have a direct effect on tubular handling of lithogenic substances.[5] A recent longitudinal study reported associations between antibiotic use and higher risk of stones predominantly in children and young adults;[6] however, that study did not account for potential differences in dietary intakes, and the results may have been due in part to higher rates of abdominal imaging in individuals taking more antibiotics as the study likely included asymptomatic, incidentally diagnosed kidney stones. We analyzed the independent, prospective association between duration of antibiotic use and the subsequent risk of a first symptomatic kidney stone in two large cohorts of adult women. We also evaluated the association between antibiotic use and 24h urine composition in a subsample of the cohorts with available 24h urine data.

Methods

Study population

The Nurses' Health Study (NHS) I cohort was started in 1976 with the enrollment of 121,700 female nurses aged 30 to 55 years; the NHS II cohort was started in 1989 with the enrollment of 116,430 female nurses aged 25 to 42 years. For both cohorts, participants completed a detailed questionnaire with information on lifestyle, medical history and medications. The questionnaire was subsequently mailed every two years to update information. Follow-up of eligible person-time has exceeded 90% in each cohort. 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 antibiotic use

In 2004 (for NHS I) and 2005 (NHS II) participants were asked to report the cumulative amount of time they used antibiotics between age 20 to 39 years and between 40 to 59 years (NHS I) or 40 to 49 years (NHS II), excluding skin creams, mouthwash, or isoniazid. To ensure that the assessment of antibiotic use in our longitudinal study occurred before an incident kidney stone, the baseline of our analysis was 2004 for NHS I and 2005 for NHS II. Categories for total time of antibiotic use during these age periods were "none", "less than 15 days", "15 days to 2 months", "2-4 months", "4 months to 2 years", "2-3 years", "3-5 years", "more than 5 years". Thus, we could not determine whether longer periods of reported previous antibiotic use represented a single episode of exposure, or the sum of multiple, shorter episodes. Participants also were asked about the most common reason for their antibiotic use ("respiratory infection", "Urinary tract infection" [UTI], "Acne/ Rosacea", "Chronic bronchitis", "Dental", or "Other").

Assessment of kidney stones

The study outcome was an incident, symptomatic kidney stone. Participants reporting a kidney stone were asked to complete a supplementary questionnaire with information about date of occurrence and accompanying symptoms. The supplementary questionnaire also queried presence or absence of urinary tract infection during or preceding the kidney stone event. Self-reported kidney stone diagnosis was found to be reliable by medical record review of a sample of 1,634 participants (confirmed in ≥95% who completed the supplementary questionnaire).[7] In a subsample of the study population with stone composition reports, the stone type was predominantly calcium oxalate (>50%) in 77% of participants in the NHS I, and 79% of participants in the NHS II cohort.[7]

Assessment of other covariates

Starting in 1986 (for NHS I) and 1991 (for NHS II), participants completed a food-frequency questionnaire (FFQ) with information on average use of more than 130 foods and more than 20 beverages in the previous year. Intake of individual nutrients was calculated from the frequency of consumption of foods and from data on the content of the relevant nutrients obtained from the US Department of Agriculture, except for oxalate intake which

was directly measured in foods by capillary electrophoresis.[8] The FFQ has been sent every 4 years and also queries the use of multivitamins as well as individual supplements such as calcium and vitamin D. Information on nutrients obtained with the FFQ was validated in the cohorts.[9,10]

Information about age, BMI, history of diabetes, and use of thiazides was obtained from the biennial questionnaires.

Assessment of urine chemistries

Urine samples were collected in three separate cycles. In the first, which spanned from 1994 to 1999, eligible participants were ≤65 years of age in the NHS I with no history of cancer or cardiovascular disease. In the second, performed in 2003, eligible participants were ≤75 years of age and had no history of cancer (other than nonmelanoma skin cancer). The third cycle was performed in 2009 only in the NHS II cohort, and eligible participants were ≤55 years old, white race, with no history of hypertension, coronary heart disease, or cancer. Urine samples collected in the first two cycles were analyzed by Mission Pharmacal (San Antonio, TX), whereas the samples collected in the third cycle were analyzed by the Litholink Corporation (Chicago, IL). Participants with possible over- or undercollections (defined as urinary creatinine excretion in the top or bottom 1% of the nonstone-formers distribution) were removed from the analysis. For participants who provided more than one collection, the first sample was analyzed.

Statistical analysis

The study design was prospective; information on antibiotic use was collected before the incident kidney stone. Total time of antibiotic use during the two age periods in each cohort was categorized into “no use”, “less than 2 months” and “2 months or more” for statistical analysis. These categories were selected to examine clinically significant differences in previous antibiotic use while preserving adequate case numbers in each category. Time at risk started from the date of return of the 2004 (NHS I) or 2005 (NHS II) questionnaire and participants were followed until the development of a symptomatic kidney stone, an asymptomatic kidney stone, cancer, death, or end of follow-up (2012 for NHS I, 2011 for NHS II), whichever occurred first. While the end of follow-up was a censoring event, an asymptomatic kidney stone, cancer, and death were competing events. Participants with a history of cancer (except non-melanoma skin cancer) or a history of kidney stones at baseline were excluded from the study. Cause-specific hazards models, treating competing events as censoring, were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), using the “no use” as the referent category. Models were adjusted for age, BMI, history of diabetes, use of thiazides, use of calcium supplements, intake of alcohol, dietary intakes of calcium, magnesium, oxalate, potassium, sodium, animal protein, vitamin D and total fluid intake. Further adjustment was performed for bisphosphonate use and (for NHS II) menopausal status. Effect modification by dietary oxalate and calcium intake (above or below the cohort-specific medians) was investigated. All the models were repeated after exclusion of participants reporting concurrent urinary tract infection at the time of stone diagnosis or as the main reason for antibiotic use. Results from the two cohorts were pooled by random-effects meta-analysis using the DerSimonian and Laird method.[11]

The association between antibiotic use and urine composition was assessed in a cross-sectional manner with general linear models adjusted for age, kidney stone status, BMI, use of alcohol, dietary intake of oxalate, calcium, magnesium, potassium, animal protein, total fluid, supplemental use of calcium, urinary creatinine and sodium. Information was obtained from the questionnaires closest in time to the date of urine collection.

Analyses were performed with SAS version 9.4. The research protocol for this study was reviewed and approved by the Brigham and Women's Hospital institutional review board.

Results

A total of 112,324 participants remained in the study group (46,336 from NHS I and 65,988 for NHS II) as reported in the flow diagram (Figure 1). Baseline characteristics of the study population are reported in Tables 1 and 2 and Tables S1 and S2. Compared with those taking no antibiotics at age 40-49/59 years, those taking antibiotics for a total of 2 months or more during this age period were younger in NHS I, had higher mean BMI and fluid intake and a greater prevalence of hypertension and diabetes and greater use of thiazides. The main reasons for antibiotic use were respiratory infections (52% in NHS I, 53% in NHS II), urinary tract infections (11% in NHS I, 15% in NHS II), and dental infections (10% in NHS I, 7% in NHS II).

For the 40-49/59 years group analysis, there were 1,059 incident kidney stones during a cumulative follow-up of 694,194 person-years. The association between antibiotic use and risk of incident kidney stones is reported in Table 3. There was a significantly higher risk of incident kidney stones with antibiotic use of 2 months or more (pooled multivariable-adjusted HR, 1.48; 95% CI, 1.12-1.96).

Similarly, for the 20-39 years group analysis the pooled multivariable-adjusted HR was 1.36 (95% CI, 1.00-1.84). The estimates were similar after exclusion of participants reporting urinary tract infection at the time of stone diagnosis or as the main reason for antibiotic use, as well as after further adjustment for bisphosphonate use and menopausal status. There was no significant effect modification by dietary intake of oxalate or calcium.

The association between antibiotic use and urine composition was studied in a subsample of 5,010 participants with at least one 24h urine collection available for analysis (Table 4). Urine composition was generally similar across groups except for marginally lower urine pH, calcium, and citrate among those taking antibiotics for 2 months or more.

Discussion

We found a higher risk of developing a first symptomatic kidney stone for users of antibiotics in two prospective cohorts of women. The association was statistically significant after adjusting for potential confounders. We speculate that this association may be due to changes in the intestinal microbiome composition induced by antibiotic use. The intestinal microbiome has been suggested to modulate the intestinal handling of calcium and oxalate; [12] for example, the presence and relative abundance of *Oxalobacter formigenes*, a specialized oxalate-degrading microorganism, has been correlated with a history of kidney

stones,[13] although the oral administration of *Oxalobacter formigenes* has shown inconsistent results in randomized controlled trials.[14–16] More generally, stone formers have been shown to have systematically different intestinal microbiome composition compared with non-stone formers,[3,4] suggesting that alterations in the intestinal flora might predispose to stone formation. The intestinal microbiome has also been implicated in the intestinal handling of calcium through direct effects on the mechanisms of calcium absorption.[12] Some antibiotics could also directly precipitate and form stones due to their low solubility in urine.[17]

Another explanation for the potential lithogenic effects of antibiotics is through the induction of changes in tubular handling of lithogenic substances described for certain antibiotics such as cotrimoxazole and ceftazidime, which have been shown to increase urinary excretion of phosphate and calcium, thus increasing the urinary supersaturation for calcium salts.[5]

In our own data, we found a tendency to lower urine citrate and pH among those taking antibiotics for more than 2 months in the past but we did not find a difference in urine oxalate or calcium. However, the temporal relationship between antibiotic use and urine collection in the cohorts was not standardized, i.e. about 2,500 urine collections in NHS II were obtained after the antibiotic exposure question, whereas for NHS I part of the urine collections were obtained during the time period of interest.

In the literature, there is a scarcity of data regarding the association between use of antibiotics and risk of kidney stones, except for a recent report[6] in which participants with kidney stones were identified through administrative codes. Recognizing the known tendency of kidney stones to recur, the use of administrative codes would not allow to easily distinguish between a first stone event, a recurrence, and the expulsion of a previous stone. Furthermore, that study lacked information on dietary intakes (although our own data do not suggest a large impact of diet on the association between exposure to antibiotics and risk of stones) and likely included asymptomatic, incidentally diagnosed kidney stones that may have been detected as a result of more frequent imaging in individuals taking antibiotics.

Our study has limitations, including the observational design, the relatively large span of time between antibiotic use and urine collection, and the enrollment of only women in NHS. In addition, antibiotic use was not validated, and we did not have information on the types of antibiotics used.

In conclusion, use of antibiotics for a total of two months or more during early to middle adulthood is independently associated with a higher subsequent risk of developing kidney stones in later life. Our data provide an additional reason to minimize the unnecessary use of antibiotics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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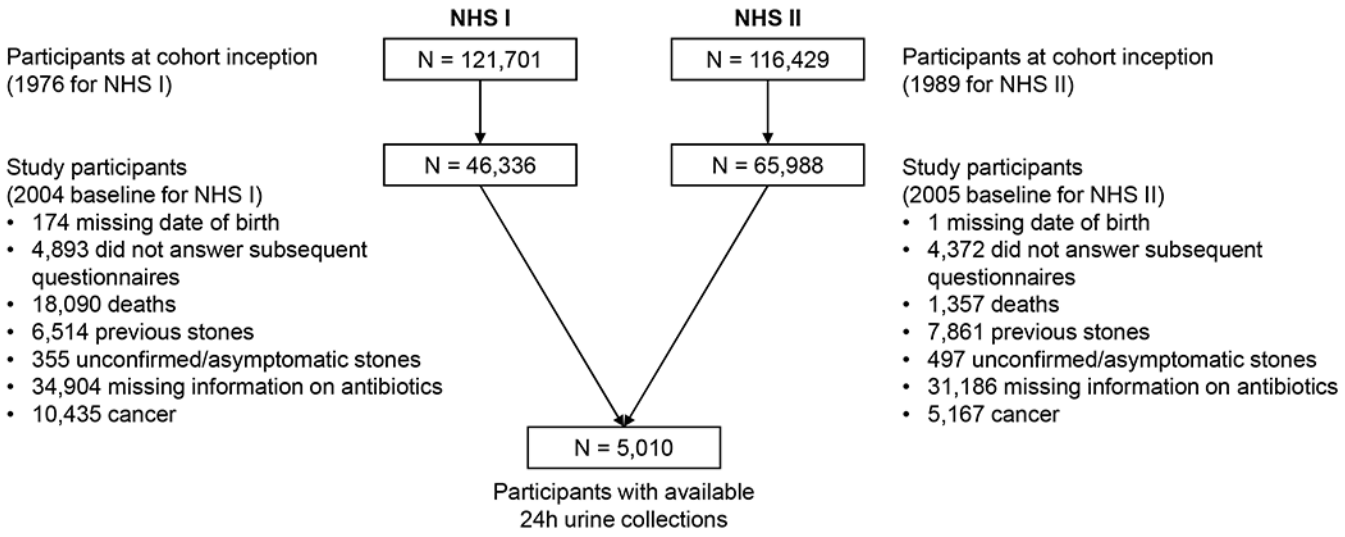

Figure 1.
Flowchart of the study

Table 1.

Baseline characteristics by antibiotic use at ages 40-59 – Nurses' Health Study I

	No antibiotic use (n = 3,817)	**Duration of Antibiotic Use**	
		<2 months (n = 38,001)	**>=2 months (n = 4,518)**
Age, years*	70.8 (6.9)	68.6 (6.7)	66.8 (6.6)
BMI, kg/m^2	25.7 (4.7)	26.6 (5.3)	27.2 (5.9)
History of hypertension, %	50.2	56.9	61.8
Thiazide diuretic use, %	13.7	18.2	22.0
History of diabetes, %	7.4	9.7	12.3
Daily intake			
Total fluid, mL	1,694 (712)	1,752 (689)	1,815 (704)
Alcohol, g	6.4 (11.1)	6.2 (10.8)	5.5 (10.3)
Dietary calcium, mg	862 (336)	858 (319)	861 (316)
Supplemental calcium, mg	583 (532)	634 (524)	698 (536)
Animal protein, g	44.7 (14.4)	46.3 (13.6)	47.1 (13.5)
Potassium, mg	3,080 (625)	3,082 (591)	3,071 (595)
Sodium, mg	1,959 (434)	1,996 (427)	2,015 (419)
Oxalate, mg	178 (107)	175 (100)	172 (93)
Magnesium, mg	369 (126)	374 (123)	386 (128)
Vitamin D, IU	542 (343)	572 (336)	589 (337)
Vitamin C, mg	346 (382)	374 (396)	418 (411)
Sucrose, g	38.1 (16.6)	37.9 (15.7)	38.0 (15.3)

BMI, body mass index. Values are mean +/− SD or percentages and are standardized to the age distribution of the study population.

*Value is not age adjusted

Table 2.

Baseline characteristics by antibiotic use at ages 40-49 – Nurses' Health Study II

	No antibiotic use (n = 6,631)	**Duration of Antibiotic Use**	
		<2 months (n = 51,795)	**>=2 months (n = 7,562)**
Age, years*	48.6 (5.2)	50.5 (4.6)	50.4 (4.2)
BMI, kg/m^2	25.8 (5.4)	27.2 (6.3)	28.4 (7.2)
History of hypertension, %	18.3	24.7	32.9
Thiazide diuretic use, %	5.3	8.3	12.2
History of diabetes, %	2.3	3.9	6.6
Daily intake			
Total fluid, mL	1,748 (888)	1,768 (906)	1,849 (910)
Alcohol, g	6.0 (9.7)	5.8 (9.5)	5.0 (9.6)
Dietary calcium, mg	954 (343)	937 (328)	936 (329)
Supplemental calcium, mg	468 (497)	488 (504)	532 (521)
Animal protein, g	54.0 (16.9)	54.9 (15.9)	55.5 (15.9)
Potassium, mg	3,220 (640)	3,194 (601)	3,160 (615)
Sodium, mg	2,228 (492)	2,267 (472)	2,291 (473)
Oxalate, mg	197 (125)	194 (124)	189 (108)
Magnesium, mg	375 (124)	374 (121)	378 (126)
Vitamin D, IU	494 (336)	498 (334)	516 (342)
Vitamin C, mg	300 (372)	305 (370)	337 (409)
Sucrose, g	40.0 (17.5)	40.2 (17.4)	40.7 (18.4)

BMI, body mass index. Values are mean +/− SD or percentages and are standardized to the age distribution of the study population.

*Value is not age adjusted

Table 3.

Association between antibiotic use and risk of incident kidney stones

	No antibiotic use	Duration of Antibiotic Use	
		<2 months	>=2 months
40 to 49/59 years			
Nurses Health Study I			
- Cases	20	285	44
- Person-years	26,555	271,480	32,155
- Age-adjusted HR	1.00 (reference)	1.28 (0.81,2.01)	1.57 (0.92, 2.67)
- MV-adjusted HR	1.00 (reference)	1.26 (0.80, 1.99)	1.51 (0.88, 2.58)
Nurses Health Study II			
- Cases	58	549	103
- Person-years	36,791	285,664	41,549
- Age-adjusted HR	1.00 (reference)	1.23 (0.93, 1.61)	1.59 (1.15, 2.20)
- MV-adjusted HR	1.00 (reference)	1.18 (0.89, 1.55)	1.47 (1.06, 2.04)
Pooled cohorts			
- Age-adjusted HR	1.00 (reference)	1.24 (0.98, 1.57)	1.58 (1.20, 2.09)
- MV-adjusted HR	1.00 (reference)	1.20 (0.95, 1.52)	1.48 (1.12, 1.96)
20 to 39 years			
Nurses Health Study I			
- Cases	39	272	38
- Person-years	48614	255,481	26,094
- Age-adjusted HR	1.00 (reference)	1.13 (0.81, 1.60)	1.43 (0.91,2.26)
- MV-adjusted HR	1.00 (reference)	1.14 (0.81, 1.60)	1.44 (0.91,2.28)
Nurses Health Study II			
- Cases	28	518	164
- Person-years	15,604	278,045	70,355
- Age-adjusted HR	1.00 (reference)	1.05 (0.72, 1.54)	1.33 (0.89, 1.99)
- MV-adjusted HR	1.00 (reference)	1.04 (0.71, 1.94)	1.29 (0.86, 1.94)
Pooled cohorts			
- Age-adjusted HR	1.00 (reference)	1.10 (0.85, 1.42)	1.37 (1.02, 1.86)
- MV-adiusted HR	1.00 (reference)	1.09 (0.85, 1.41)	1.36 (1.00, 1.84)

Multivariate models adjusted for age, BMI, history of diabetes, use of thiazides, use of calcium supplements, intake of alcohol, dietary intakes of calcium, magnesium, oxalate, potassium, sodium, animal protein, vitamin D and total fluid intake

Table 4.

Adjusted mean values of urine chemistries by antibiotic use

	No antibiotic use	Duration of Antibiotic Use	
		<2 months	>=2 months
40 to 49/59 years			
Nurses' Health Study I			
- Calcium (mg/d)	197	187	178
- Oxalate (mg/d)	28	29	29
- Citrate (mg/d)	642	627	609
- Volume (L/d)	1.7	1.8	1.8
- pH	6.05	6.03	5.91 *
Nurses' Health Study II			
- Calcium (mg/d)	205	205	193
- Oxalate (mg/d)	30	30	30
- Citrate (mg/d)	816	782 *	754 *
- Volume (L/d)	2.0	2.0	2.0
- pH	6.17	6.14	6.15
20 to 39 years			
Nurses' Health Study I			
- Calcium (mg/d)	185	189	174
- Oxalate (mg/d)	29	29	30
- Citrate (mg/d)	629	629	624
- Volume (L/d)	1.7	1.8	1.8
- pH	6.09	6.02	5.95 *
Nurses' Health Study II			
- Calcium (mg/d)	201	205	199
- Oxalate (mg/d)	30	30	30
- Citrate (mg/d)	819	783	778
- Volume (L/d)	1.9	2.0	2.0
- pH	6.18	6.15	6.16

Values adjusted for age, kidney stone status, BMI, use of alcohol, dietary intake of oxalate, calcium, magnesium, potassium, animal protein, total fluid, supplemental use of calcium, urinary creatinine and sodium

* $p<0.05$