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Nephrolithiasis and Risk of Incident Bone Fracture

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Purpose: Higher urine calcium is a common feature of calcium nephrolithiasis and may be associated with lower bone mineral density in individuals with kidney stones (KS). However, previous population based studies of KS and risk of bone fracture report conflicting results. We examined independent associations between history of KS and incident fracture.

Materials and Methods: We conducted prospective studies in the Nurses' Health Study (N=107,001 women; 32 years of follow-up) and the Health Professionals Follow-up Study (N=50,982 men; 26 years of follow-up). We excluded pre-menopausal women, men < 45 years old, and individuals who reported osteoporosis at baseline. The study outcomes were incident wrist (distal radius) or incident hip (proximal femur) fractures due to low or moderate trauma. Cox proportional hazards regression was used to adjust for multiple factors including age, race, BMI, thiazide use, supplemental calcium, and dietary intakes.

Results: There were 4940 wrist and 2391 hip fractures in women and 862 wrist and 747 hip fractures in men (all incident). The multivariable-adjusted relative risk (MVRR) of incident wrist fracture in participants with a history of KS compared with participants without KS was 1.18 (95% CI 1.04-1.34) in women and 1.21 (95% CI 1.00-1.47) in men. The pooled MVRR of wrist fracture was 1.20 (95% CI 1.08-1.33). The MVRR of incident hip fracture in participants with KS was 0.96 (95% CI 0.80-1.14) in women and 0.92 (95% CI 0.74-1.14) in men. The pooled MVRR of hip fracture was 0.94 (95% CI 0.82-1.08).

Conclusions: Nephrolithiasis is associated with a significantly higher risk of incident wrist but not hip fracture in women and men.

Kidney stones are a major cause of morbidity and are common: the prevalence of nephrolithiasis in the United States increases with age but in the overall population is about 11% for men and 7% for women.[1] Calcium nephrolithiasis accounts for more than 80% of kidney stones.[2]

Some previous studies reported lower bone mineral density in individuals with a history of nephrolithiasis compared with those without,[3-6] and bone demineralization in calcium stone formers may be related to higher urine calcium.[7, 8] Previous reports also suggest that individuals with nephrolithiasis may have higher risk of bone fracture.[9-11] A recent study utilizing data from the Health Improvement Network (THIN) in the United Kingdom compared more than 50,000 individuals with diagnostic codes for urolithiasis with over 500,000 participants without such codes. The risk of incident bone fracture in individuals with a history of kidney stones was 10% higher in men and varied by age in women (the highest relative risk was 1.52 for women aged 30 to 39 years).[9]

However, the association between nephrolithiasis and bone fracture remains unclear for several reasons. First, the THIN study was not able to adjust for race or diet.[9] Because blacks are less likely to form kidney stones than whites[1] and also are less likely to have bone fracture,[12] it is possible the THIN results reflect a higher proportion of blacks in the referent group. It is also possible that associations in THIN were due to differences in diet. For example, lower intakes of fruits and vegetables and higher intakes of red and processed meats and sugar sweetened beverages are associated with higher risk of nephrolithiasis and fracture.[13-17] Second, not all longitudinal studies have identified kidney stones as a risk factor for bone fracture. A recent study in the Women's Health Initiative (WHI) included nearly 10,000 women with a self-reported history of kidney stones followed for over 8 years and reported no independent association between nephrolithiasis and incident fracture.[18] Finally, no population based study to date has excluded fractures due to major trauma. Bone fractures in the setting of high trauma likely occur regardless of kidney stone status.

To delineate independent associations between history of nephrolithiasis and the subsequent risk of incident bone fracture due to low or moderate trauma, we conducted prospective analyses in the Nurses' Health Study (NHS) and the Health Professional Follow-up Study (HPFS) cohorts.

MATERIALS and METHODS

Source population

In 1976, 121,700 female registered nurses between the ages of 30 and 55 years enrolled in NHS by completing and returning an initial questionnaire that provided detailed information on medical history, life style, and medications. This cohort, like HPFS, is followed by biennial mailed questionnaires, which include inquiries about the incidence of newly diagnosed diseases. For this study, we started follow-up in 1980, since before that date we lacked information on diet. In 1986, 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians between the ages of 40 and 75 years enrolled in HPFS by completing and returning an initial questionnaire.

Study population

The primary analysis included postmenopausal women and, to make the two cohorts more consistent, men 45 years of age or older. Women who were premenopausal at baseline entered the analysis at the biennial questionnaire when they reached menopause, and men younger than 45 years old entered when they turned 45. Participants with previous wrist, hip, or vertebral fractures and those with a history of self-reported osteoporosis were excluded at the start of the analysis. A total of 101,319 NHS and 50,893 HPFS participants were included in the wrist fracture analysis and 107,001 NHS and 50,982 HPFS participants were included in the hip fracture analysis. Fewer participants contributed to the wrist fracture analysis because assessment of wrist fracture ended before assessment of hip fracture.

Ascertainment of kidney stones

Questions about history of kidney stones were first asked in 1992 for NHS and in 1986 for HPFS. Thus, the current analysis was limited to NHS participants who answered questionnaires in 1992 or later. Subsequent biennial questionnaires asked about history of kidney stones in the previous 2 years. Participants reporting an incident kidney stone were mailed a supplementary questionnaire asking about the date of occurrence and symptoms. The self-reported diagnosis was confirmed in 97% of participants who completed the supplementary questionnaire in 2 separate validation studies.[19, 20] In a subset of individuals with nephrolithiasis and available kidney stone composition reports, 77% of NHS and 86% of HPFS participants had a stone that contained $\geq$ 50% calcium oxalate.[17]

Ascertainment of wrist and hip fractures

Participants reported wrist and hip fractures on biennial questionnaires, which also assessed information on bone site, date of fracture, and circumstances under which the fracture occurred. Wrist fracture assessment ended in 2004 for NHS and in 2008 for HPFS. The primary outcomes of the study were fractures of the distal radius (wrist) or proximal femur (hip) that occurred in the setting of low or moderate trauma. Fractures due to motor vehicle accidents, horseback riding, skiing, and other high trauma events were excluded because major trauma can cause fracture regardless of bone mineral density. In a validation study in NHS, medical record review confirmed reported fractures in all 30 sampled cases.[21]

Ascertainment of diet

The semiquantitative food-frequency questionnaire (FFQ) asks about the average use of more than 130 individual foods and 22 beverages during the previous year, and has been mailed to study participants every 4 years. The FFQ also includes an open-ended section. The reproducibility and validity of the FFQ in NHS and HPFS have been documented.[22, 23]

Nutrient intake was computed from the reported frequency of consumption of each specified unit of food and from USDA data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake.[24, 25] The intakes of supplemental calcium and vitamin D in multivitamin or isolated form were determined by the brand, type, and frequency of reported use.

Ascertainment of non-dietary covariates

Information on age, weight and height was obtained on the baseline questionnaire. Self-reported weight was updated every two years. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Self-reported weight has been validated in NHS and HPFS.[26] Smoking, physical activity, thiazide diuretic use, postmenopausal hormone use, and histories of osteoporosis, cancer, cardiovascular disease, and diabetes all were assessed via biennial questionnaires. Self-reported age at menopause and type of menopause were previously validated.[27] Physical activity (in metabolic equivalent task scores) ascertained by biennial questionnaire was highly correlated with physical activity diaries (r=0.79) in a similar cohort of women.[28] Race was self-reported.

Statistical analysis

Person-months of follow-up for each eligible participant were allocated according to exposure status at the start of each two-year follow-up period. For NHS, person-months of follow-up were counted until the date of incident fracture, death, or May 31 of 2004 (wrist fracture analysis) or 2012 (hip fracture analysis). For HPFS, person-months of follow-up were counted until the date of incident fracture, death, or January 31 of 2008 (wrist fracture analysis) or 2012 (hip fracture analysis). In each analysis, participants were censored during follow-up if they reported any other fracture.

Cox proportional hazards regression was used to adjust for the following covariates: age (continuous), race (white, black, Asian, multiracial, other), body mass index (6 categories), smoking (past, current, or never), physical activity (quintiles), use of thiazide diuretics (yes or no), postmenopausal hormone use (in NHS; yes or no), histories of cancer, cardiovascular disease, and diabetes (all yes or no), alcohol use (seven categories), multivitamin use (yes or no), calcium supplement use (four categories), intakes of total (i.e., supplemental plus dietary) vitamin D and vitamin A (quintiles), caffeine intake (quintiles), and dietary calcium, animal protein, potassium, and vitamin K (all in quintiles). The covariates included in the multivariate Cox models were updated throughout the analysis.

We calculated 95% confidence intervals for all hazard ratios (relative risks). All P values are two-tailed. The results of the two cohorts were pooled using random effects meta-analysis. All data were analyzed by using SAS software, version 9.3 (SAS Institute). The research protocol for this study was reviewed and approved by the Partners HealthCare institutional review board.

RESULTS

Baseline characteristics of NHS and HPFS participants with and without a history of kidney stones are shown in Table 1. Both cohorts were greater than 90% white. Compared with women without a history of kidney stones, NHS participants with nephrolithiasis were slightly younger, had higher BMI, had higher rates of thiazide use, diabetes mellitus, and current smoking, and had lower intakes of calcium and potassium. Baseline differences between HPFS participants with and without a history of kidney stones were similar to NHS, except men with nephrolithiasis were older, had lower levels of physical activity, were less likely to be current smokers, and had lower intakes of alcohol, vitamin D, and animal protein.

Age and multivariable-adjusted relative risks of incident wrist fracture by kidney stone history are shown in Table 2. There were 4,940 incident wrist fractures during 1,653,035 person-years of follow-up in NHS and 862 incident wrist fractures during 955,834 person-years of follow-up in HPFS. The median age at wrist fracture was 61.0 years for NHS and 65.3 years for HPFS. After adjusting for age, race, BMI, smoking, physical activity, use of thiazide diuretics, postmenopausal hormone use (NHS only), history of cancer, history of cardiovascular disease, history of diabetes, alcohol use, multivitamin use, calcium supplement use, and intakes of vitamin D, dietary calcium, animal protein, potassium, vitamin K, caffeine, and vitamin A, the relative risk of incident wrist fracture in participants with a history of kidney stones compared with participants without was 1.18 (95% CI 1.04 to 1.34) in NHS and 1.21 (95% CI 1.00 to 1.47) in HPFS. The pooled multivariable-adjusted relative risk was 1.20 (95% CI 1.08 to 1.33).

Age and multivariable-adjusted relative risks of incident hip fracture by kidney stone history are shown in Table 3. There were 2,391 incident hip fractures during 2,104,892 person-years of follow-up in NHS and 747 incident hip fractures during 1,014,158 person-years of follow-up in HPFS.

The median age at hip fracture was 71.0 years for NHS and 75.8 years for HPFS. After multivariable adjustment, the relative risk of incident hip fracture in participants with a history of kidney stones compared with participants without was 0.96 (95% CI 0.80 to 1.14) in NHS and 0.92 (95% CI 0.74 to 1.14) in HPFS. The pooled multivariable-adjusted relative risk was 0.94 (95% CI 0.82 to 1.08).

We performed a variety of secondary analyses in NHS and HPFS. Exclusion of participants with missing dietary data during follow-up did not materially change the results (the proportion of person-time contributed by participants with missing diet was 25% for NHS and 21% for HPFS). Including men and women with self-reported osteoporosis at baseline did not change the results, nor did including wrist or hip fractures sustained as a result of high impact trauma. There were not statistically significant interactions with age, BMI, or calcium intake, and inclusion of premenopausal women and men younger than 45 years old yielded risk estimates for fracture similar to those obtained in the primary analysis. Finally, additional adjustment for sugar-sweetened soda intake did not materially change the results.

DISCUSSION

In two prospective cohorts, we observed a modest association between a history of kidney stones and higher risk of incident wrist fracture. Our analysis accounted for differences in race, body size, dietary intakes and other factors that may affect both kidney stone formation and fracture risk.

The potential mechanisms underlying the observed association between kidney stones and higher risk of wrist fracture in our study are unknown. However, some previous studies have reported lower bone mineral density in individuals with a history of nephrolithiasis compared with those without.[3-6] Higher urinary calcium levels (even in ranges considered normal) are a major risk factor for nephrolithiasis,[29] and it is possible that bone demineralization in calcium stone formers may be related to higher losses of urine calcium.[7, 8] In a study of 46 stone formers and their first degree relatives followed for 3 years, the correlation between higher baseline 24-hour calcium excretion and subsequent decrease in femoral neck bone mineral density was -0.37 (P = 0.02).[7] This relation was independent of calcium intake and 24-hour urine markers of dietary acid load, such as sulfate.[7]

The reasons for the disparate results for wrist and hip fracture in our study are unclear. Some of the discrepancy may be due to the older age at which study participants sustained hip compared with wrist fractures. In the THIN study, the risk of incident fracture in individuals with a history of kidney stones was 10% higher in men but varied by age in women,[9] with the highest risk occurring at younger ages. For example, the hazards ratio for fracture in women with kidney stones was 1.52 for those aged 30 to 39 years but was 1.01 for those aged 80 to 89 years.[9] Age-related variability in associations between nephrolithiasis and fracture could be due in part to age-dependent differences in kidney stone composition. A recent study reported that the proportion of calcium compared with uric acid kidney stones decreased with older age,[30] and it is possible that calcium nephrolithiasis is associated with higher fracture risk while uric acid nephrolithiasis is not.

Our results differ from the recent WHI study, which reported no independent associations between self-reported nephrolithiasis and incident fracture risk in postmenopausal women.[18] However, the WHI study did not examine wrist fracture as a specific outcome. In addition, self-reported kidney stones have not been validated in WHI. The possibility of kidney stone misclassification is raised by the higher kidney stone incidence rate in blacks compared with whites in WHI,[18] a racial difference not observed in other large well characterized populations.[1]

Our study has limitations. First, most kidney stones and fractures were not adjudicated by medical record review. However, self-reported kidney stones and fractures were validated in the study population. Second, we do not have data on kidney stone composition or 24-hour urine calcium excretion for the majority of stone formers in our study. However, it is likely that the majority of individuals with nephrolithiasis had predominantly calcium stones.[17] Third, we did not examine vertebral fracture. Some data suggest that higher urine calcium in stone formers is associated with lower bone mineral density preferentially in trabecular rich bone.[8] If true, the magnitude of potential associations between kidney stone history and vertebral fracture may be larger than for wrist and hip fracture. Finally, we did not assess bone mineral density.

CONCLUSIONS

A history of kidney stones is independently associated with a higher risk of incident wrist fracture in two large cohorts of women and men. The disparate results for wrist and hip fracture in our study suggest that the fracture risk associated with kidney stones may vary by skeletal site. Clinicians should ensure that patients with calcium nephrolithiasis are appropriately screened for osteoporosis, and future studies should explore the mechanisms underlying associations between kidney stones, lower bone mineral density, and higher risk of wrist fracture.

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Table 1. Age-Adjusted Baseline Characteristics of Postmenopausal Women (NHS) and Men $\geq$ 45 years (HPFS) by History of Nephrolithiasis.*

	KS History +	KS History -	P value
NHS			
Number (%)	1,205 (3.4)	34,266 (96.6)	
Age, years	51.5	51.7	<0.001
White (%)	93.6	92.9	0.41
BMI, kg/m^2	25.7	24.7	<0.001
Current thiazide use (%)	14.6	11.4	0.001
History of diabetes (%)	4.5	2.8	<0.001
Use of postmenopausal hormones (%)	16.5	17.2	0.43
Physical activity (METs)	14.2	14.1	0.97
Smoking status (%)			
Never	41.3	45.5	0.02
Past	27.0	26.3	0.70
Current	31.7	28.2	0.006
Intakes			
Alcohol (gm/d)	6.3	6.6	0.41
Total vitamin D (IU/d)	346	339	0.46
Total calcium (mg/d)	708	741	0.002
Potassium intake (mg/d)	2757	2816	0.003
Animal protein intake (gm/d)	62.3	62.6	0.73
HPFS			
Number (%)	3,457 (8.7)	36,285 (91.3)	
Age, years	59.4	58.3	<0.001
White (%)	90.8	90.6	0.84
BMI, kg/m^2	25.3	25.0	<0.001
Current thiazide use (%)	14.2	11.6	<0.001
History of diabetes (%)	4.6	3.9	0.04
Physical activity (METs)	18.9	20.1	0.03
Smoking status (%)			
Never	47.0	44.9	0.01
Past	44.2	45.1	0.31
Current	8.8	9.9	0.02
Intakes			
Alcohol (gm/d)	10.1	11.9	<0.001
Total vitamin D (IU/d)	395	426	<0.001
Total calcium (mg/d)	824	916	<0.001
Potassium intake (mg/d)	3397	3509	<0.001
Animal protein intake (gm/d)	67.1	68.2	0.001

*Baseline was 1980 for NHS and 1986 for HPFS. The total number of participants included in the analysis was greater than at baseline, since women entered follow-up when they became menopausal and men entered follow-up when they turned age 45.

Note: Values expressed as means, unless otherwise specified. BMI = Body mass index.

Table 2. Relative Risk of Incident Wrist Fracture According to Kidney Stone History in Postmenopausal Women (NHS) and Men ≥ 45 years of age (HPFS).*

	Person-years	Wrist Fracture	Age-adjusted RR	Multivariate RR**
NHS				
Stones –	1,575,697	4680	1.00 (reference)	1.00 (reference)
Stones +	77,338	260	**1.18** (1.04, 1.34)	**1.18** (1.04, 1.34)
HPFS				
Stones –	841,258	738	1.00 (reference)	1.00 (reference)
Stones +	114,576	124	**1.22** (1.01, 1.48)	**1.21** (1.00, 1.47)
Pooled cohorts				
Stones –	--	--	1.00 (reference)	1.00 (reference)
Stones +	--	--	**1.19** (1.07, 1.32)	**1.20** (1.08, 1.33)

*Participants who reported history of osteoporosis or bone fracture at the start of analysis were excluded.

**Relative risks (RR) include 95% confidence intervals in parentheses. The multivariate model includes age, race, body mass index, smoking, physical activity (quintiles), use of thiazide diuretics (yes or no), postmenopausal hormone use (women), history of cancer, history of cardiovascular disease, history of diabetes, alcohol use (seven categories), multivitamin use, calcium supplement use (four categories), and intakes of vitamin D, dietary calcium, animal protein, potassium, vitamin K, caffeine, and vitamin A (all in quintiles).

Table 3. Relative Risk of Incident Hip Fracture According to Kidney Stone History in Postmenopausal Women (NHS) and Men ≥ 45 years of age (HPFS).*

	Person-years	Hip Fracture	Age-adjusted RR	Multivariate RR**
NHS				
Stones –	1,997,294	2258	1.00 (reference)	1.00 (reference)
Stones +	107,598	133	**1.02** (0.85, 1.21)	**0.96** (0.80, 1.14)
HPFS				
Stones –	889,665	645	1.00 (reference)	1.00 (reference)
Stones +	124,493	102	**0.94** (0.76, 1.16)	**0.92** (0.74, 1.14)
Pooled cohorts				
Stones –	--	--	1.00 (reference)	1.00 (reference)
Stones +	--	--	**0.98** (0.86, 1.13)	**0.94** (0.82, 1.08)

*Participants who reported history of osteoporosis or bone fracture at the start of analysis were excluded.

**Relative risks (RR) include 95% confidence intervals in parentheses. The multivariate model includes age, race, body mass index, smoking, physical activity (quintiles), use of thiazide diuretics (yes or no), postmenopausal hormone use (women), history of cancer, history of cardiovascular disease, history of diabetes, alcohol use (seven categories), multivitamin use, calcium supplement use (four categories), and intakes of vitamin D, dietary calcium, animal protein, potassium, vitamin K, caffeine, and vitamin A (all in quintiles).

Key of Definitions for Abbreviations

HPFS = Health Professionals Follow-up Study

NHS = Nurses' Health Study

BMI = Body mass index

FFQ = Food-frequency questionnaire

THIN = the Health Improvement Network

WHI = Women's Health Initiative