Risk of Fracture in Urolithiasis: A Population-Based Cohort Study Using the Health Improvement Network

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Abstract

Background and objectives Studies have shown decreased bone mineral density in individuals with urolithiasis, but their burden of fracture remains unclear. This study sought to determine whether urolithiasis is associated with increased fracture risk across the lifespan and to delineate sex effects.

Design, setting, participants, & measurements A population-based retrospective cohort study using The Health Improvement Network was performed. The median calendar year for the start of the observation period was 2004 (1994–2012). This study identified 51,785 participants with ≥1 of 87 diagnostic codes for urolithiasis and 517,267 randomly selected age-, sex-, and practice-matched participants. Cox regression was used to estimate the hazard ratio (HR) for first fracture. Fractures identified using diagnostic codes were classified by anatomic site.

Results Median age was 53 years, and 67% of participants were men, confirming their greater urolithiasis burden. Median time from urolithiasis diagnosis to fracture was 10 years. The HR for fracture associated with urolithiasis differed by sex and age (P for interactions, $P \leq 0.003$). In men, the adjusted HR was greatest in adolescence (1.55; 95% confidence interval [95% CI], 1.07 to 2.25) with an overall HR of 1.10 (95% CI, 1.05 to 1.16). Urolithiasis was associated with higher fracture risk in women aged 30–79 years (HR, 1.17–1.52), and was highest in women aged 30–39 years (HR, 1.52; 95% CI, 1.23 to 1.87). Peak background fracture rates were highest in boys aged 10–19 years and in women aged 70–79 years. The incidence per 10,000 person-years in participants with versus without urolithiasis was 392 versus 258 in male participants aged 10–19 years, and 263 versus 218 in women aged 70–79 years. Distribution of fracture site within sex did not differ between participants with versus without urolithiasis.

Conclusions Urolithiasis was associated with higher incident fracture risk. The significantly higher risk at times of peak background fracture incidence in adolescent boys and elderly women has profound public health implications.

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Introduction

Urolithiasis is a common condition with a prevalence of 3%–5% and a lifetime risk of 11% in men and 5.6% in women (1,2). The incidence has been increasing worldwide, possibly related to the rising prevalence of obesity and diabetes (3,4). Forty percent of patients recur within 5 years, and 75% recur within 20 years (2,5). Approximately 90% of individuals with recurrent urolithiasis have a demonstrable metabolic abnormality, with hypercalciuria accounting for 40%–60% of identifiable abnormalities (6,7).

Idiopathic hypercalciuria (IH) can lead to negative calcium balance, which can compromise bone modeling. Consequently, it is not surprising that studies have reported decreased bone mineral density (BMD) in patients with IH (8). Most (9–11) but not all (12) studies have demonstrated reduced BMD among individuals with urolithiasis. Sites of observed bone loss include the spine, femoral neck, and radius (8–10,13–15). Low BMD has not been consistently observed in studies of normocalciuric formers of renal calculi

(8,16). Interestingly, one study showed that low BMD of the spine and femoral neck correlated with increasing urinary calcium losses in those with a history of renal calculi, but not in those who had never formed a calculus (17).

It remains unclear whether the low BMD observed in individuals with urolithiasis contributes to an increased burden of fracture. Studies of fracture risk in this population are limited. One retrospective cohort study of 624 patients with symptomatic urolithiasis demonstrated that the risk of vertebral fracture was four times greater than expected based on rates in the general population, but found no increased risk in fractures of the hip, pelvis, humerus, or forearm (18). A subsequent cross-sectional study of 793 adults with a history of renal calculi from the Third National Health and Nutrition Examination Survey (NHANES III) found that men, but not women, were more likely to report a history of spine and wrist fractures (15).

The study of disease-associated fractures requires a valid source of fracture data and attention to age-, sex-,

and geographic-related variations in fracture risk. The Health Improvement Network (THIN) database has been used to characterize the risk of fracture associated with several chronic conditions and drug exposures in adults and children (19–26). The objectives of this large population-based study were to determine whether urolithiasis is associated with a higher risk of incident fracture and to delineate age and sex effects. A secondary aim was to assess the distribution of fracture sites in participants with compared to those without urolithiasis.

Materials and Methods
Study Design/Data Source
We conducted a population-based retrospective cohort study using the THIN database. THIN provides deidentified data from the electronic medical records of 553 general practices in the United Kingdom, including demographics, diagnoses, prescriptions, procedures, and select laboratory measures, and comprises data from >10 million people (27). Medical diagnoses are recorded using Read codes, the standard classification system in the United Kingdom (28). The January 2012 version of the database was used. The study adhered to the Declaration of Helsinki, was approved by the THIN Scientific Review Committee and determined by the Institutional Review Board of the University of Pennsylvania to meet eligibility criteria for institutional review board exemption authorized by 45 CFR §46.101, category 4.

Study Population
Participants with acceptable records for research based on checks performed by the data vendor and at least one of 87 Read codes consistent with urolithiasis (Supplemental Material) were included as exposed. The most frequently used codes were as follows: renal calculus, renal stone, extracorporeal shockwave lithotripsy for renal calculus, calculus of kidney, and ureteric calculus. For each participant with urolithiasis, up to 10 randomly selected participants without urolithiasis who were matched on age (3-year age groups up to 30 years and 5-year age groups thereafter), sex, and practice were included as unexposed. To mitigate against misclassification bias, participants who only had codes for renal colic, bladder/lower urinary tract calculi (presumed infectious), infectious calculi, hypercalciuria, or nephrocalcinosis (n=61,270) were excluded from the entire cohort (see the Supplemental Material for these 49 codes). We excluded 221 participants because of the absence of an associated date(s) for the urolithiasis event(s) and 1504 participants whose last code for urolithiasis was before 1970. Data on participants aged ≥90 years were excluded.

The timing of initial diagnosis of urolithiasis for all exposed participants was the date of their first entry of a urolithiasis code. The start of the observation period for ascertainment of incident fractures in these participants was the latest of this initial Read code for urolithiasis, 6 months after registration with the practice, and the date that the practice started using the Vision software as the electronic medical record. Requiring that the period of observation start after 6 months of registration and use of Vision software is standard practice for ascertainment of incident fracture events in the THIN database and avoids inclusion of prevalent events (i.e., fractures that occurred before the observation period) (29).

Because the urolithiasis code may have preceded either 6 months of registration or the practice's use of the Vision software, the time from urolithiasis exposure to fracture outcome may exceed the observation period. Historical fractures were not an exclusion criterion, but were adjusted for in the analysis. The observation period for unexposed participants started on the same date as that of their matched exposed participant. The median calendar year for the start of observation was 2004 (range 1994–2012). The observation period ended with the earliest of the following: last collection date for the practice, or when applicable, transfer out of the practice, death, or initial fracture event. Given the retrospective observational nature of this medical records database, participants are not recruited for participation. Transfer out of a given practice is a routine occurrence, and the reasons for transferring out of a practice are unknown, but are likely nondifferential.

Fracture Outcome
Fractures were identified using consistent Read diagnostic codes and classified according to anatomic site as follows: vertebral, skull/face, pelvis, rib/thorax, clavicle/scapula, humerus/elbow, forearm/wrist, hand, femur/hip, lower leg/ankle, and foot. We excluded surgically induced fractures and fractures attributed to birth trauma or metastatic bone disease. We also excluded codes indicative of follow-up care for fracture due to concerns about timing of the associated fracture event. For the minority (1.5%) of first fracture events for which there were codes for ≥2 sites on the same date, the fracture was categorized as multisite. Fractures were categorized by the site-specific code if both site-specific and nonspecific codes were entered for the date of first fracture.

Covariates
The following potential confounding conditions and medications were evaluated: diabetes mellitus, gout, cystic fibrosis, prematurity/low birth weight, primary hyperparathyroidism, sarcoidosis, inflammatory bowel disease (IBD), fat malabsorption/pancreatic insufficiency, chronic immobility/neurogenic bladder, systemic corticosteroids, loop diuretics, and topiramate. Covariate exposure was defined as having a consistent Read code or prescription recorded by the start of observation with the exception of conditions inherently present from birth, which were defined by ever having a consistent diagnostic code.

Statistical Analyses
Descriptive statistics were reported as the median and interquartile range for continuous variables and frequencies for categorical variables. Group differences in categorical variables were assessed using the chi-square test. Cox proportional hazards regression was used to assess the association between urolithiasis and incident fracture. Because the median observation period was 4.7 years, using age at start of observation would generate misleading information regarding age-specific hazards. Therefore, the data set had multiple records for the majority (93%) of participants, with each record representing the time followed in a given year of life. We examined multiplicative interactions among age, sex, and urolithiasis. Stratified Cox regression models were used to

estimate age- and sex-specific hazard ratios (HRs) with 95% confidence intervals (95% CIs). Multivariable Cox regression analysis was used to assess confounding by covariates. A two-sided P value of <0.05 was considered statistically significant. Analyses were performed using STATA 13.0 software (Stata Corporation, College Station, TX).

Results

Cohort Characteristics

Our cohort comprised 51,785 participants with urolithiasis and 517,267 unexposed participants (Table 1). Consistent with the established epidemiology of urolithiasis (1,2), there were twice as many men with urolithiasis than women. A history of fracture before start of observation was more common among participants with urolithiasis than among unexposed participants ($P<0.001$). All of the covariates selected *a priori* as potential confounding conditions and medications were significantly more prevalent among the participants with urolithiasis (all $P<0.001$).

Fracture Incidence

Over a median observation period for ascertainment of incident fracture of 4.7 years in both groups, 3524 incident fractures (118 per 10,000 person-years) occurred in participants with urolithiasis compared with 29,590 in those without urolithiasis (101 per 10,000 person-years). For participants with urolithiasis, the median time from the initial code for urolithiasis to the first incident fracture event was 10.0 years (interquartile range, 4.2, 18.4). The proportion of participants with urolithiasis censored at death (7.6%) and transfer out of their practice (19.6%) was similar to that of

unexposed participants (7.7% and 20.6%, respectively). Figure 1 shows the incidence of first fracture in participants with versus without urolithiasis by sex and in each decade of life. Of note, the incidence in boys aged 10–19 years with urolithiasis was 392 per 10,000 person-years compared with 258 per 10,000 person-years in their unexposed peers. The incidence was 263 per 10,000 person-years among women aged 70–79 years with urolithiasis versus 218 per 10,000 person-years in unexposed women of this age.

Fracture Site

Site of fracture differed by sex ($P<0.001$), with hand fractures being the most common among male participants (17%) and forearm/wrist the most common site (21%) among female participants. However, among both sexes, the distribution of fracture site did not differ between those with and without urolithiasis (Figure 2). Further stratification by decade of life revealed no differences in the sex-specific distribution of fracture site in participants with versus without urolithiasis.

Cox Regression Analyses of Fracture Risk

A statistically significant three-way interaction was found among urolithiasis, sex, and age ($P=0.003$). Therefore, all analyses were stratified on sex and age (Figure 3). A statistically significant higher risk of fracture was found in male participants aged 10–19, 40–49, 50–59, and 80–89 years with urolithiasis. However, among male participants, there was no interaction between age and urolithiasis, indicating that the risk of fracture associated with urolithiasis did not vary with age; therefore, an overall HR of 1.13 (95% CI, 1.08 to 1.18) for fracture in male participants was reported. Among

Table 1. Cohort characteristics

Characteristic	Urolithiasis (n=51,785)	No Urolithiasis (n=517,267)	P Value
Age at start of follow-up (yr)	53 (40, 64)	53 (40, 64)	
Male sex	66.9	66.8	
Country			
England	78	78	
Ireland	3	3	
Scotland	13	13	
Wales	5	5	
Follow-up time (yr)	4.7 (2.1, 9.0)	4.7 (2.1, 8.7)	
History of prior fracture	21.0	18.8	<0.001
Covariate exposures			
Diabetes mellitus	9.2	6.1	<0.001
Gout	3.9	3.0	<0.001
Cystic fibrosis	0.07	0.03	<0.001
Prematurity/low birth weight	0.22	0.15	<0.001
Primary hyperparathyroidism	0.70	0.07	<0.001
Sarcoidosis	0.37	0.22	<0.001
Inflammatory bowel disease	1.95	0.91	<0.001
Malabsorption	0.11	0.04	<0.001
Chronic immobility	1.22	0.75	<0.001
Covariate medications			
Loop diuretic	7.0	6.0	<0.001
Systemic corticosteroids	14.6	13.1	<0.001
Topiramate	0.14	0.06	<0.001

Data are presented as the median (interquartile range) or percentage. P values were calculated with the chi-square test.
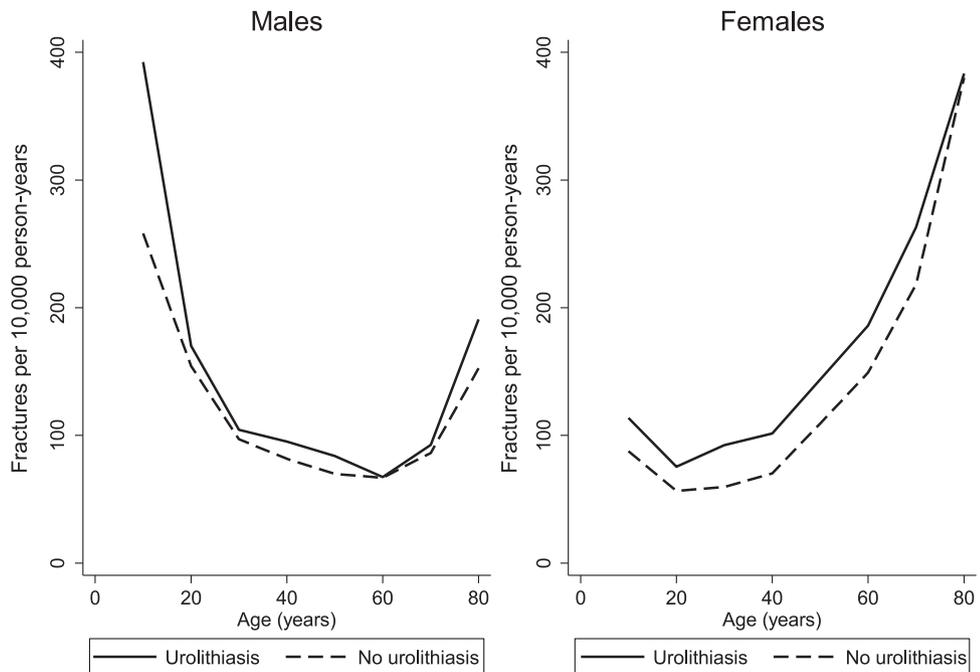
Figure 1. | **Fracture incidence by decade of age and sex in participants with and without urolithiasis.**
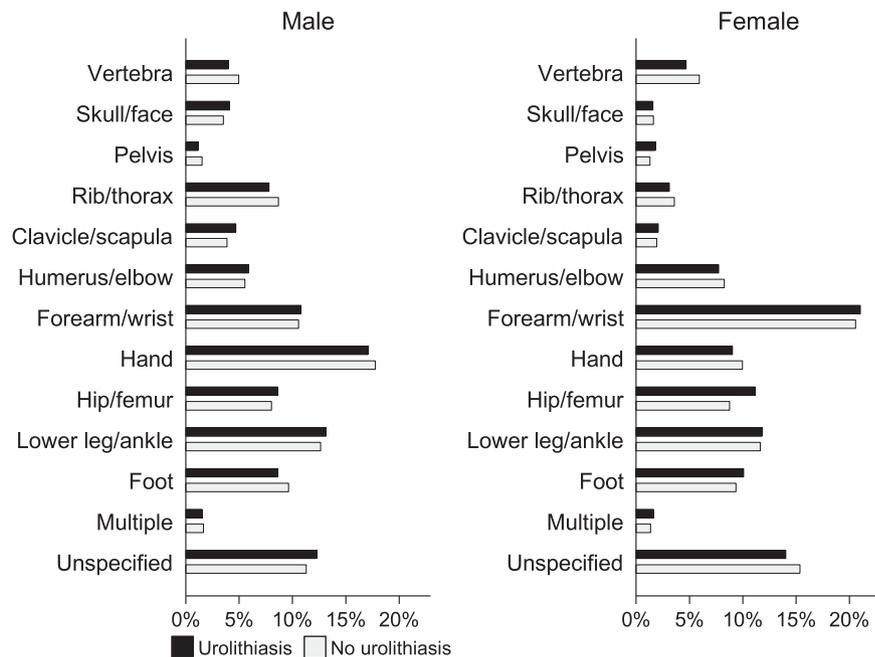

Figure 2. | **Distribution of fracture site in participants with and without urolithiasis.**

female participants, the risk of fracture associated with urolithiasis did vary according to age, with the excess risk being more pronounced among younger individuals (*P* for interaction, *P*<0.001). Urolithiasis was associated with a significantly higher risk of fracture from the third through seventh decades of life in women, greatest in women aged 30–39 years (HR, 1.55; 95% CI, 1.26 to 1.90).

For male and female participants, each covariate was assessed separately using a base model that included urolithiasis

and age. All covariates with a *P* value of <0.05 were then included in sex-specific multivariable models. In male participants, the following were significantly associated with fracture adjusted for age and urolithiasis: diabetes (HR, 1.26; *P*<0.001), gout (HR, 1.20; *P*<0.001), prematurity/low birth weight (HR, 1.62; *P*=0.02), primary hyperparathyroidism (HR, 1.56; *P*=0.05), IBD (HR, 1.25; *P*=0.001), immobility/neurogenic bladder (HR, 1.78; *P*<0.001), loop diuretics (HR, 1.81; *P*<0.001), systemic corticosteroids (HR, 1.38; *P*<0.001),
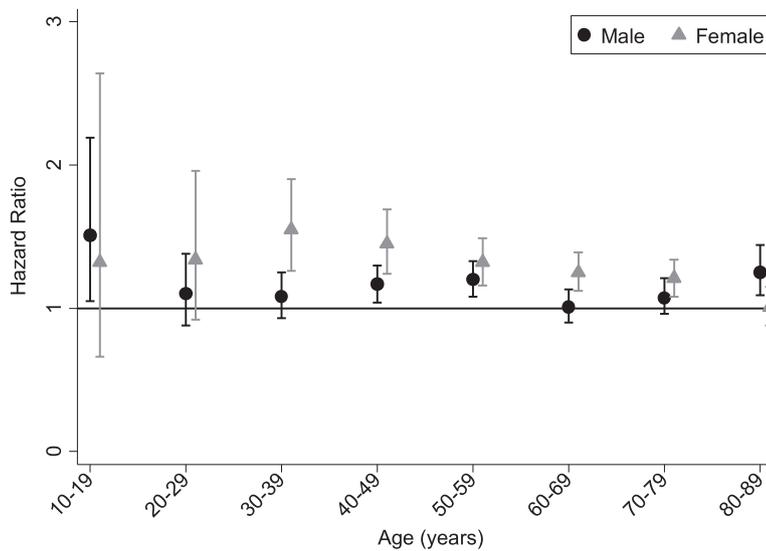
Age (years)	Males				Females			
	HR	95% CI	p value	N	HR	95% CI	p value	N
10-19	**1.51**	**(1.05, 2.19)**	**0.03**	3692	1.32	(0.66, 2.64)	0.43	3264
20-29	1.10	(0.88, 1.38)	0.40	22,748	1.34	(0.92, 1.96)	0.13	18,567
30-39	1.08	(0.93, 1.25)	0.32	67,367	**1.55**	**(1.26, 1.90)**	**<0.001**	38,593
40-49	**1.17**	**(1.04, 1.30)**	**0.008**	107,485	**1.45**	**(1.24, 1.69)**	**<0.001**	52,265
50-59	**1.20**	**(1.08, 1.33)**	**<0.001**	133,061	**1.32**	**(1.16, 1.49)**	**<0.001**	56,788
60-69	1.01	(0.90, 1.13)	0.88	132,480	**1.25**	**(1.12, 1.39)**	**<0.001**	54,693
70-79	1.07	(0.96, 1.21)	0.23	90,251	**1.21**	**(1.08, 1.34)**	**0.001**	41,926
80-89	**1.25**	**(1.09, 1.44)**	**0.002**	37,029	1.01	(0.88, 1.15)	0.90	22,257
Overall	**1.13**	**(1.08, 1.18)**	**<0.001**		Not applicable[a]			

Figure 3. | **HR for fracture associated with urolithiasis by age and sex.** [a]Given the presence of a statistically significant interaction between age and urolithiasis in female participants (*i.e.,* the HR for fracture associated with urolithiasis in female participants differed according to age), an overall HR result cannot be reported for female participants. 95% CI, 95% confidence interval; HR, hazard ratio.

and topiramate (HR, 3.92; $P<0.001$). In female participants, the following were associated with fracture adjusted for age, urolithiasis, and their interaction: diabetes (HR, 1.25; $P<0.001$), IBD (HR, 1.17; $P=0.04$), immobility/neurogenic bladder (HR, 1.28; $P=0.003$), loop diuretics (HR, 1.36; $P<0.001$), systemic corticosteroids (HR, 1.30; $P<0.001$), and topiramate (HR, 2.59; $P<0.001$). Cystic fibrosis, sarcoidosis, and malabsorption were not associated with fracture independent of urolithiasis and age in either sex. Table 2 shows the final multivariable Cox regression models for male and female participants. Urolithiasis remained significantly associated with fracture with minimal attenuation of the HR after adjustment for all of the aforementioned covariates. The overall adjusted HR in male participants was 1.10 (95% CI, 1.05 to 1.16). Urolithiasis remained associated with a higher risk of fracture from the third through seventh decades in women, with the excess risk being more pronounced in younger women, with adjusted HRs of 1.52 (95% CI, 1.23 to 1.87) in women aged 30–39 years versus 1.17 (95% CI, 1.05 to 1.30) in women aged 70–79 years.

In both male and female participants, history of prior fracture was independently associated with higher risk of incident fracture (HR, 1.75 and 1.95 in male and female participants, respectively; $P<0.001$), but did not confound the association between urolithiasis and fracture. There was a higher risk of fracture with advancing calendar year of start of observation (HR, 1.02 and 1.01 per year in male and female participants, respectively; $P\leq0.001$), but adjustment for this secular trend did not affect model findings in terms of the HR associated with urolithiasis. Adjustment for calcium and vitamin D use did not attenuate the HR for fracture associated with urolithiasis in either sex. Furthermore, adjustment for thiazide use, with or without adjustment for hypertension, also did not change model findings. Thiazide use was not protective; it was associated with a higher risk of fracture in male participants (HR, 1.08; $P=0.003$) and was not associated with fracture in female participants. The significant association with fracture risk is consistent with confounding by indication. In the 197,067 participants with BMI data within 2 years of start of observation, adjustment for BMI did not affect model findings. Finally, we performed a sensitivity analysis limited to the 17,016 incident urolithiasis participants and their 170,121 matched unexposed participants, and urolithiasis remained significantly associated with higher fracture risk in multivariable Cox regression (overall HR, 1.11 in male participants; $P=0.03$) (HR, 1.59 and 1.34 in women aged 30–39 years and aged 70–79 years, respectively; $P\leq0.01$).

Table 2. Sex-stratified multivariable Cox regression analyses of fracture risk associated with urolithiasis

Variable	HR (95% CI)	P Value
Male participants (n=380,338)		
Urolithiasis	1.10 (1.05 to 1.16)	<0.001
Age (yr)	1.00 (0.99 to 1.00)	<0.001
Diabetes	1.17 (1.11 to 1.25)	<0.001
Gout	1.12 (1.04 to 1.20)	0.002
Prematurity/low birth weight	1.47 (0.98 to 2.20)	0.06
Primary hyperparathyroidism	1.37 (0.88 to 2.12)	0.16
Inflammatory bowel disease	1.10 (0.96 to 1.26)	0.18
Immobility/neurogenic bladder	1.63 (1.42 to 1.88)	<0.001
Loop diuretic	1.67 (1.57 to 1.78)	<0.001
Corticosteroid	1.32 (1.26 to 1.37)	<0.001
Topiramate	3.50 (2.30 to 5.31)	<0.001
Female participants (n=188,714)		
Urolithiasis	1.97 (1.57 to 2.47)	<0.001
Age (yr)	1.04 (1.03 to 1.04)	<0.001
Urolithiasis $\times$ age	0.99 (0.99 to 1.00)	<0.001
Diabetes	1.18 (1.11 to 1.26)	<0.001
Inflammatory bowel disease	1.07 (0.92 to 1.23)	0.39
Immobility/neurogenic bladder	1.16 (0.99 to 1.36)	0.07
Loop diuretic	1.29 (1.22 to 1.36)	<0.001
Corticosteroid	1.25 (1.20 to 1.31)	<0.001
Topiramate	2.38 (1.43 to 3.95)	0.001

HR, hazard ratio; 95% CI, 95% confidence interval.

Discussion

Urolithiasis has been identified as a risk factor for fracture in two prior studies (15,18). A retrospective cohort study (18) of 624 patients with symptomatic urolithiasis found a 4-fold greater risk of first vertebral fracture than expected in the general population. A subsequent cross-sectional study of 793 NHANES III participants (15) found that men, but not women, who reported a history of renal calculi were more likely to report a history of spine and wrist fractures. Our study has several strengths that expand upon this earlier work, conclusively confirm and define this association, and fill gaps in the previous literature. First, the robust size of the THIN database allowed us to study >50,000 participants with urolithiasis and compare them with >500,000 unexposed participants who were matched on age, sex, and practice. Second, we were able to delineate age and sex effects. The longitudinal nature of our study allowed us to assess the risk of incident fracture in each decade of life. Third, we were able to more clearly discern any differences in the distribution of fracture site. Finally, THIN has been shown to be representative of the larger United Kingdom population (30), making our findings generalizable.

We observed that for participants with urolithiasis, the median time from initial entry of a diagnosis code for urolithiasis to the first fracture was 10 years. Urolithiasis remained significantly associated with fracture after adjustment for potential confounding conditions and medications. Although there was no statistically significant interaction between urolithiasis and age on risk of fracture among male participants, the greatest risk was noted among male participants aged 10–19 years (55% higher), with a 10% increased risk overall. The risk of fracture associated with urolithiasis did vary according to age among women; there

was a significantly higher risk of fracture from the third through seventh decades of life, with the highest risk in women aged 30–39 years (52% higher) and gradually declining until age 70–79 years (17% higher). We did not observe any difference in the distribution of fracture site in participants of either sex with versus without urolithiasis.

Our data cannot establish a causal mechanism, but clearly confirm the association between urolithiasis and risk of subsequent fracture. Current evidence points to an association between IH and diminished BMD. Several studies demonstrated that IH in childhood is associated with low BMD (31,32), suggesting that life-long hypercalciuria may compromise bone health and increase fracture risk. In addition, studies in postmenopausal women with primary osteoporosis have reported a 10%–19% prevalence of hypercalciuria (33,34).

Given that urolithiasis is common, our finding of its significant association with higher risk of fracture has profound implications for both patient outcomes and economic burden. Although our data suggest that the greatest excess fracture risk was in women aged 30–39 years, the greatest public health burden arises from the higher risk at times of peak background fracture incidence (258 and 218 per 10,000 person-years in boys aged 10–19 years and women aged 70–79 years), with an additional 134 and 45 fractures per 10,000 person-years in these age groups, respectively.

Thiazides and alkali therapy are the mainstays of treatment for urolithiasis associated with hypercalciuria and hypocitraturia, respectively. Several prospective studies in older adults have shown that thiazide use is associated with reduced hip fracture incidence (35) and increased BMD (36,37). Similarly, one study has shown increased vertebral

and femoral neck BMD in osteopenic women treated with potassium citrate compared with controls (38).

Our study has several limitations. The THIN database does not include data on race, and only a subset of the participants had BMI data. However, adjustment for BMI, even in this reduced sample of the cohort, did not attenuate the association between urolithiasis and fracture. There were too few fracture events in children aged <10 years with urolithiasis to interpret the data in this group. Given that the median time from urolithiasis diagnosis to incident fracture was 10 years, the expected burden of urolithiasis-associated fracture in the first decade of life is likely lower. Because the exposure of urolithiasis was based on Read codes, there was potential for misclassification of exposure and underestimation of subclinical vertebral fractures. However, this would likely bias our results towards the null. The lack of dietary intake and physical activity data limit the evaluation of these relevant factors. The practice pattern of calcium restriction in urolithiasis may have influenced findings in participants diagnosed before the 1990s; however, urolithiasis remained significantly associated with fracture in the sensitivity analysis restricted to incident urolithiasis participants and their matched unexposed participants. The earliest year for the initial urolithiasis code in these participants was 1994 (≥2000 in 92%). Although adjustment for thiazide use did not change the finding of the association between urolithiasis and fracture, at the start of observation, only 1394 (2.7%) urolithiasis participants were prescribed a thiazide without a coexisting diagnosis of hypertension, limiting the ability to assess a potential protective effect of this therapy for the presumed indication of hypercalciuria. Finally, because of the low frequency of Read codes in the THIN database for urinary metabolic abnormalities, such as hypercalciuria, hypocitraturia, or hyperoxaluria (<1200 entries), and nephrocalcinosis (<1100 entries), we were unable to characterize which predisposing cause(s) of urolithiasis were associated with risk of fracture.

Urolithiasis and fragility fractures remain formidable health problems worldwide. The link between the two remains underappreciated, underdiagnosed, and undertreated. Our data highlight the importance of this association. Given that the time from initial diagnosis of urolithiasis to first fracture was a decade and that the excess risk affected all skeletal sites, there is reason to believe that we might possibly be able to intervene during this critical interval and decrease the risk of future fracture.

Disclosures

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