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Fracture risk among patients with urolithiasis: A population-based cohort study

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Fracture risk among patients with urolithiasis: A population-based cohort study. In a population-based retrospective cohort study, 624 Rochester, Minnesota residents with an initial symptomatic episode of urolithiasis in 1950 to 1974 were followed for 11,909 person-years for subsequent age-related fractures. During this period of observation, the number of patients with a first vertebral fracture was over four times the number expected on the basis of vertebral fracture incidence rates in the general population of Rochester [standardized morbidity ratio (SMR), 4.3; 95% confidence interval, 3.4 to 5.3]. The risk of vertebral fracture was elevated among men as well as women, and was associated with increasing age and with the use of corticosteroids for more than six months. However, vertebral fracture risk was increased nearly fourfold (SMR 3.9; 95% confidence interval, 3.0 to 4.9) among the urolithiasis patients without such exposure, which suggests that corticosteroids do not completely account for the association with vertebral fractures. There was no increase in the risk of hip, pelvis, proximal humerus or distal forearm fractures in this cohort of patients, and their survival was not impaired. Additional studies are needed to define the pathophysiology of vertebral fractures among patients with urolithiasis.

Many medical and surgical conditions are important causes of bone loss and fractures [1], and urolithiasis has long been numbered among these disorders [2, 3]. Renal stones complicate bone resorptive conditions and may also result from renal hypercalciuria, which has likewise been associated with reduced bone density [4–6]. On the other hand, bone density may be normal among urolithiasis patients with hyperabsorption of dietary calcium [7, 8] who could thus be protected from osteoporotic fractures. Most studies, however, have found only modest reductions in bone density among hypercalciuria patients generally [9]. To complicate matters further, some forms of urolithiasis therapy involve efforts to lower dietary calcium intake, and reduced calcium intake has been associated with bone loss [10, 11] as well as an increased risk of fractures in some studies, though not others [12–15]. Conversely, other types of therapy may lead to increased serum calcium levels [16] and reduced bone demineralization [17]. Thiazide therapy, for example, has generally been associated with increased bone density and a reduced risk of fractures [18]. To date, there have been no population-based studies of fracture risk following the initial diagnosis of urolithiasis that would allow the practical implications of these diverse influences to be determined. The aim of the present study was to estimate the incidence of age-related fractures among Rochester, Minnesota residents first diagnosed with urolithiasis during the 25-year period of 1950 to 1974, and to compare this with the incidence in the general population. In addition, we sought to evaluate the impact of other risk factors for fracture, which may be independent and/or additive to the effects of kidney stones.

Key words: Urolithiasis, osteoporosis, hip fracture, vertebral fracture, distal forearm fracture.

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METHODS

Population-based epidemiologic research can be conducted in Rochester because medical records for the entire population are available from almost all providers of care. Most of the endocrinological, surgical and trauma care is provided by the Mayo Clinic, which has maintained a common medical record with its two large affiliated hospitals (St. Marys and Rochester Methodist) for 90 years. This dossier-type record contains both inpatient and outpatient data, and the diagnoses and surgical procedures recorded in these records are entered into a computerized index [19]. Medical records of the other providers who serve the local population, most notably the Olmsted Medical Group and its affiliated Olmsted Community Hospital, are indexed into the same system (the Rochester Epidemiology Project) and are also available for study [20]. Using this unique database, 672 Rochester residents were identified who presented with their first episode of symptomatic (renal colic, hematuria, dysuria) urolithiasis in the time period of 1950 to 1974, as described in detail elsewhere [21]. Patients with asymptomatic stones found incidentally or those who presented primarily for urinary tract infections were not included. For the present analysis, we excluded five patients who had only possible rather than probable or definite renal stones and three patients who died within 30 days of their first episode of urolithiasis. We excluded an additional 32 patients who, upon further review, were found to have exclusions (infection, staghorn calculus), and 8 with an earlier episode of urolithiasis prior to 1950 or before immigrating to Rochester. Thus, the final study population numbered 624 individuals.

These subjects were then followed forward in time through their linked medical records in the community (retrospective cohort study) until death or the most recent clinical contact. For

each subject, all inpatient and outpatient medical records at any local provider of health care were searched for the occurrence of specific fractures. Mayo Clinic records, for example, contain the details of every inpatient hospitalization at its two hospitals, every outpatient office or clinic visit, emergency room and nursing home care, as well as radiographic reports and pathology reports, including autopsies [19]. Emphasis was on fractures at the skeletal sites usually associated with osteoporosis, and these were recorded regardless of whether they occurred before or after the recognition of urolithiasis. The records contained the clinical history and the radiologist's report of each fracture, but the original roentgenograms were not available for review. Thus, the diagnosis of vertebral fracture was accepted on the basis of a radiologist's report of compression or collapse of one or more thoracic or lumbar vertebrae. All fractures were classified according to the circumstances of the injury. By convention, falls from standing height or less were considered moderate trauma, while motor vehicle accidents and falls from heights were deemed severe trauma. Ascertainment of the fractures of interest is believed to be complete except for vertebral fractures, some of which are never diagnosed [22].

The influence of urolithiasis on fracture incidence was evaluated using three basic methods of analysis. In the primary analysis, we calculated standardized morbidity ratios (SMRs), comparing the number of fractures that were observed at the selected skeletal sites (based on the first fracture of a given type per person) to the number expected in this cohort during their follow-up in the community. Patients were deleted from the analysis for specific fracture sites who had experienced that particular type of fracture after the age of 35 years but prior to the initial recognition of urolithiasis. Expected numbers of fractures were derived by applying age- and sex-specific incidence rates from the general population for these fractures to the age- and sex-specific person-years of follow-up in the cohort. Incidence rates from the general population of Rochester were available for fractures of the proximal femur [23], distal forearm [24], proximal humerus [25], pelvis [26] and vertebrae [22]. Ninety-five percent confidence intervals for the SMRs were calculated assuming that the expected rates are fixed and the observed fractures follow a Poisson distribution [27].

In the second method of analysis, the cumulative incidence of new fractures (1 minus survival-free-of-fracture) was projected for up to 30 years following the index date, using product-limit life table methods [28]. Cumulative incidence curves were compared using the log-rank test statistic [29]. Product-limit life table methods were also used to assess survival, with expected death rates derived from Minnesota whites of like age and gender.

Finally, the relative influence of various clinical characteristics on subsequent fracture risk was evaluated with proportional hazards models [30], using chi-square tests for the coefficients of the models and for the model likelihood ratio. Univariate relationships between the risk of any fracture due to moderate trauma, as well as any fracture of a specific type, and each clinical characteristic under consideration were first assessed. Stepwise methods with forward selection and backward elimination were then used to choose independent variables for the final model. The dependent variable was time until the first new fracture, and the independent variables were age, sex and the clinical characteristics. Drug exposures were measured as time-dependent variables. For the final multiple models, as well as for the univariate models, the assumption of proportional hazards was examined and was not violated for the variables considered.

Table 1. Characteristics of Rochester, Minnesota residents with symptomatic urolithiasis first recognized in 1950 to 1974

	N	%
Type of stone		
Calcium oxalate	158	25.3
Calcium phosphate	15	2.4
Mixed	45	7.2
Urate	8	1.3
Other	1	0.2
Unknown	397	63.6
Clinical diagnosis[a]		
Hyperuricemia/gout	146	23.4
Idiopathic hypercalciuria	47	7.5
Hyperparathyroidism	13	2.1
Small bowel resection	9	1.4
Inflammatory bowel disease	4	0.6
Sarcoidosis	1	0.2
Uncertain	428	68.6

[a] More than one diagnosis may have been reported

RESULTS

Six hundred twenty-four Rochester, Minnesota residents were first recognized with symptomatic urolithiasis in the 25-year study period and met the criteria for inclusion in this analysis. Of the total, 442 (71%) were men. The patients ranged in age from 12 to 92 years, with a median age at first diagnosis of 43.4 years (mean 44.3 years). All but four of the patients were white, reflecting the racial composition of the community. The majority of patients were diagnosed clinically (including plain films of the abdomen, excretory urograms and cystoscopy), and the type of stone was not established (Table 1). Of the 227 patients whose stones were evaluated, nearly 70% were calcium oxalate and 20% more were of mixed type, mostly calcium oxalate with phosphate or carbonate. Likewise, urolithiasis was ascribed to a particular etiology in less than one-third of the patients, mostly hyperuricemia followed by idiopathic hypercalciuria and hyperparathyroidism (Table 1). It was not possible to apply contemporary diagnostic criteria to patients evaluated over two decades ago, but none of the cases was attributed by their attending physicians to absorptive hypercalciuria or renal tubular acidosis. Among these unselected patients from the community, only 22 were begun on chronic medical therapy following this initial symptomatic episode (allopurinol therapy in 10, alkalinization of the urine in 9, neutral phosphate in 2 and probenecid for one patient with uric acid stones). Subsequently, a few others were treated with pharmacotherapy for urolithiasis (11 with neutral phosphate but none with sodium cellulose phosphate), despite the fact that 38% of the total group had at least one recurrent stone episode. However, 192 of the remaining 591 patients were on thiazide diuretics during follow-up and 22 were taking calcium supplements, although we could not link treatment specifically with their kidney stones. We made no attempt to document general recommendations with respect to changes in diet or fluid intake.

Following the initial recognition of urolithiasis, the cohort was followed for a total of 13,034 person-years for vital status, during which time 230 subjects died. Survival was slightly better ($P = 0.019$) than that expected for individuals of similar age and sex

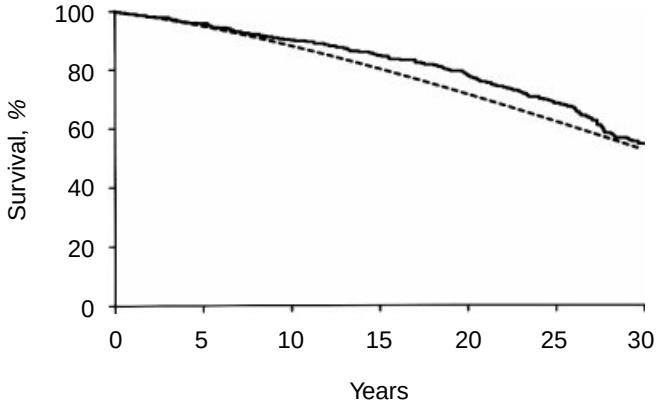

Fig. 1. Observed (solid line) and expected (dashed line) survival following the initial episode of symptomatic urolithiasis among Rochester, Minnesota, residents, 1950 to 1974.

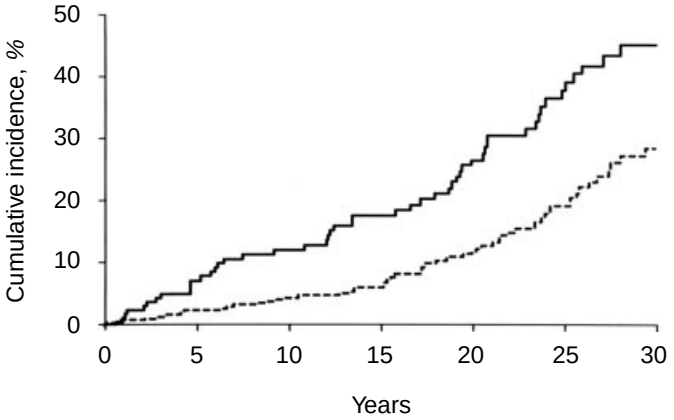

Fig. 2. Cumulative incidence of any new age-related fracture among Rochester, Minnesota men (dashed line) and women (solid line) following the initial episode of symptomatic urolithiasis, 1950 to 1974.

Table 2. Fractures by skeletal site and cause among Rochester, Minnesota residents following the initial episode of symptomatic urolithiasis, 1950 to 1974

	Fracture site				
Cause	Vertebra	Proximal humerus	Distal forearm	Pelvis	Proximal femur
Motor vehicle accident	5	1		2	
Fall from height	5	3	3	1	2
Fall from standing	7	9	19	2	15
Other trauma	5				
Spontaneous	57	1		1	2
Pathological	2				
Unknown	5	—	1	1	—
Total	86	14	23	7	19

from the general population as shown in Figure 1. Follow-up for fractures was only through the date of the last clinic visit and totaled 11,909 person-years (mean, 19.1 years per subject ± 11.5 years). Median follow-up was 19.8 years for those who died, 23.5 years for those who survived at last follow-up and 21.3 years overall. Seventy percent of the survivors had been seen within five years of the time of data collection, thus indicating a relatively stable study population. During this period of observation, 122 subjects suffered one or more of the fractures of interest. The distribution of causes by fracture site is delineated in Table 2. The majority of limb fractures were due to falls from a standing height or less, while most of the vertebral fractures occurred "spontaneously" in the course of the activities of daily living. Fracture risk increased steadily with time, reaching 16% by 20 years and 33% by 30 years following the initial episode of symptomatic urolithiasis. Because 54 of the women (30%) had one or more of these fractures compared to 68 of the men (15%), the cumulative incidence was greater among women (Fig. 2). At 30 years, the cumulative incidence was estimated at 45% for the women and only 28% for the men.

Deleting 21 individuals who had a vertebral fracture prior to their first symptomatic episode of urolithiasis, the risk of a subsequent vertebral fracture was increased over fourfold above that expected for Rochester residents generally (Table 3). The standardized morbidity ratio was relatively higher among the men (SMR 7.0; 95% CI 5.3 to 9.2) than the women (SMR 2.4; 95% CI 1.6 to 3.5), although both were statistically significantly increased. This is also reflected in the cumulative incidence of vertebral fracture in this cohort (Fig. 3), which was 25% at 30 years compared to an expected 6% ($P < 0.001$). Compared to that expected, fracture risk was not elevated at the proximal humerus (deleting 4 subjects with a prior proximal humerus fracture), the distal forearm (deleting 11 subjects with a prior distal forearm fracture), the pelvis (deleting 2 subjects with a prior pelvic fracture) or the proximal femur (deleting 3 subjects with a prior hip fracture) either in men, women or both sexes combined (Table 3).

In a multivariate analysis (Table 4), increasing age [hazard ratio (HR) per 10-year increase, 1.9; 95% CI 1.6 to 2.2] and female gender (HR 2.4; 95% CI 1.6 to 3.5) were independent predictors of the risk of any moderate trauma fracture (excluding fractures due to severe trauma and specific pathologies), as would be expected. However, corticosteroid use for more than six months was also an independent risk factor in the multivariate analysis (HR 3.6; 95% CI 1.7 to 7.6). Twenty-four patients had long-term corticosteroid exposure, while 26 others who were exposed for a shorter period of time (mean 1.8 months) were not included. Prednisone was used in the majority of cases and was indicated for a wide variety of conditions (arteritis in 5, chronic obstructive pulmonary disease in 5, asthma in 3, rheumatoid arthritis in 2, polymyalgia rheumatica in 2, transplantation in 2, and miscellaneous other conditions in 5). However, corticosteroid use mainly influenced the risk of vertebral fractures (see below). When vertebral fractures were excluded from the analysis, long-term corticosteroid use was not an independent predictor of the risk of limb fractures due to moderate trauma. For all fractures together, recurrent stones (yes vs. no) documented in 235 patients (HR 0.6; 95% CI 0.4 to 0.9) and moderate alcohol use (versus not) in 457 patients (HR 0.4; 95% CI 0.3 to 0.6) were protective in the univariate analysis (Table 4). Neither thiazide use (HR 1.4; 95% CI 0.99 to 2.1) nor calcium supplementation (HR 1.8; 95% CI 0.2 to 1.5) was associated with any reduction in fracture risk. A risk factor score that counted the number of diseases associated with secondary osteoporosis (seen in 39 patients), along with several protective conditions, was associated with an increased risk of

Table 3. Observed (Obs) fractures after the index date at selected sites in comparison with expected numbers (Exp) and standardized morbidity ratios (SMRs) among Rochester, Minnesota residents following the initial episode of symptomatic urolithiasis, 1950 to 1974

	Men				Women				Both sexes			
Fracture site	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
Vertebra	54	7.68	7.0	5.3–9.2	27	11.16	2.4	1.6–3.5	81	18.84	4.3	3.4–5.3
Proximal humerus	6	4.46	1.4	0.5–2.9	8	5.60	1.4	0.6–2.8	14	10.06	1.4	0.8–2.3
Distal forearm	7	10.10	0.7	0.3–1.4	15	13.18	1.1	0.6–1.9	22	23.28	1.0	0.6–1.4
Pelvis	3	2.69	1.1	0.2–3.2	2	3.37	0.6	0.1–2.1	5	6.06	0.8	0.3–1.9
Proximal femur	5	9.83	0.5	0.2–1.2	14	12.57	1.1	0.6–1.9	19	22.40	0.8	0.5–1.3

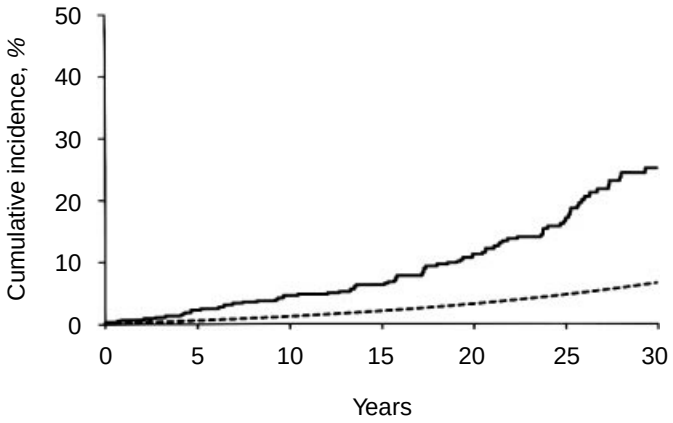

Fig. 3. Observed (solid line) and expected (dashed line) cumulative incidence of vertebral fractures among Rochester, Minnesota, residents following the initial episode of symptomatic urolithiasis, 1950 to 1974.

Table 4. Proportional hazards models[a] for the development of any age-related fracture due to moderate trauma among Rochester, Minnesota, residents following the first episode of symptomatic urolithiasis, 1950 to 1974

		Univariate			Multivariate		
Factor	*N*	β	SEβ	*P*	β	SEβ	*P*
Age	624	0.0643	0.0080	<0.001	0.0629	0.0079	<0.001
Female gender	624	0.9770	0.1984	<0.001	0.8661	0.2019	<0.001
Corticosteroid use	624	1.3296	0.3736	<0.001	1.2744	0.3811	0.003
Recurrent stones	624	−0.5467	0.2098	0.009			
Alcohol consumption	587	−0.9330	0.2113	<0.001			
Risk factor score[b]	624	0.3705	0.1344	<0.006			
Hyperuricemia/ gout	624	−0.0692	0.2175	0.75	−0.5615	0.2266	0.013

[a] Event is any age-related fracture; dependent variable is survival time (days) free of any age-related fracture.

[b] Risk factors that were observed included Paget's disease, renal failure, insulin-dependent diabetes, hyperparathyroidism, hyperthyroidism, thyroidectomy, gastric resection, chronic obstructive pulmonary disease, asthma, hemiplegia or hemiparesis, lower extremity disuse and malignancy. Non-insulin dependent diabetes, hypothyroidism and moderate alcohol use were considered protective.

fracture (HR 1.5; 95% CI 1.1 to 1.9) in the univariate analysis. None of these factors was an independent predictor of fracture risk in the multivariate analysis, however. A history of hyperuricemia or gout was not a significant risk factor for fracture in the univariate model, but was significant after adjusting for age and gender, and was an independent predictor of fracture risk in the multivariate model (HR 0.6; 95% CI 0.4 to 0.9). The protective effect of hyperuricemia was not accounted for by adjustment for body mass index.

Table 5. Proportional hazards models[a] for the development of a vertebral fracture among Rochester, Minnesota, residents following the first episode of symptomatic urolithiasis, 1950 to 1974

		Univariate			Multivariate		
Factor	*N*	β	SEβ	*P*	β	SEβ	*P*
Age	624	0.0611	0.0087	<0.001	0.0613	0.0089	<0.001
Corticosteroid use	624	1.6280	0.3772	<0.001	1.5218	0.3766	<0.001
Recurrent stones	624	−0.5000	0.2283	0.028			
Alcohol use	587	−0.5018	0.2441	0.040			

[a] Event is any vertebral fracture; dependent variable is survival time (days) free of any vertebral fracture

For vertebral fractures alone, and including all subjects in the analysis, age was a risk factor (HR per 10-year increase, 1.8; 95% CI 1.6 to 2.2) as indicated in Table 5, but gender was no longer a predictor ($P = 0.67$). The only other independent risk factor was corticosteroid use for more than six months (HR 4.6; 95% CI 2.2 to 9.6). When the 24 patients on long-term corticosteroids were excluded, however, the standardized morbidity ratio for vertebral fractures was still elevated (SMR 3.9; 95% CI 3.0 to 4.9), indicating that corticosteroid use did not account for all of the excess of vertebral fractures observed in this cohort. In the univariate analysis for vertebral fractures (Table 5), recurrent stones (HR 0.6, 95% CI 0.4 to 0.95) and alcohol use (HR 0.6; 95% CI 0.4 to 0.98) were protective, but neither was an independent predictor of vertebral fracture risk in the multivariate analysis.

DISCUSSION

The present investigation was based on an inception cohort comprised of all community residents who came to clinical attention during the study period with their first symptomatic stone episode. These patients were unselected, other than the necessity of clinical diagnosis, and 51% were attended only as outpatients [21]. As a consequence, most of the stones were not analyzed, and an underlying diagnosis was firmly established in a minority of patients. In this cohort, there was no association with distal forearm fractures, in keeping with the results of a case-control study of forearm fractures in Uppsala, Sweden [31]. Urolithiasis was not associated with the risk of distal forearm fractures among Swedish men (odds ratio 1.0; 95% CI 0.2 to 4.1); the risk among Swedish women (odds ratio 1.1; 95% CI 0.4 to 3.2) was identical to that reported here for Rochester women and neither result was statistically significant. Only 3% of the Swedish patients with a distal forearm fracture had a history of urolithiasis [31]. Likewise, the 50% reduction in hip fracture risk among

Rochester men with urolithiasis, though not statistically significant, was consistent with an earlier case-control study in this community showing that urolithiasis was associated with a decreased risk of hip fracture among Rochester men (odds ratio 0.4; 95% CI 0.2 to 0.8); only about 5% of 232 Rochester men with a moderate trauma hip fracture had a history of urolithiasis compared to 10% of a comparable group of control men [32]. However, no reduction in hip fracture risk was seen among the women with urolithiasis in the present study. Nearly a third of the cohort were prescribed thiazide diuretics at some point, and one might have expected some reduction in hip fracture risk on this basis [18]. There were not enough hip fractures to support a reliable analysis, but use of thiazide diuretics was not associated with any reduction in overall fracture risk in this cohort.

There was a substantial increase in the risk of vertebral fractures among Rochester residents with urolithiasis. This is consistent with the suggestion that there is a greater deficit of bone density at the spine than the hip in patients with nephrolithiasis [11]. Rather surprisingly, two-thirds of these fractures were in men, who account for only one-fourth of all vertebral fracture patients in the community [22]. In an earlier case-control study of vertebral fractures in men, however, no association with kidney stones was found [33]. Other than age, the only independent predictor of vertebral fractures in this study was a history of substantial corticosteroid use. This finding is not surprising since corticosteroid therapy may lead both to loss of predominantly cancellous bone [34, 35] and to renal hypercalciuria [36]. However, even excluding the cases of corticosteroid use, a history of nephrolithiasis still increased the risk of vertebral fracture, indicating an independent effect of stone disease on vertebral fracture risk. A defect in calcium absorption is aggravated by low dietary calcium intake in some patients on corticosteroids [37], and there has been concern that long-term low calcium diets, themselves, might have adverse skeletal effects in patients with urolithiasis [38]. In the case of patients with vertebral fractures specifically, there is evidence that calcium absorption is impaired [39–42], but the relative contribution of low calcium intake to fracture risk in this group has not been rigorously assessed. In a trial among patients with calcium stones due to renal hypercalciuria, however, dietary calcium restriction was associated with an increase in bone turnover [5], and elevated bone turnover has been shown to be an independent risk factor for vertebral fractures [43]. It was not possible to assess bone turnover in a medical records study such as this, but it seems clear that more research is needed into the causes of bone loss in these patients and, particularly, with respect to the potential for corticosteroid therapy to aggravate reduced osteoblast function in these patients [9].

Hyperparathyroidism has long been associated with renal stones, but this is uncommon among the patients diagnosed in recent decades, who typically are discovered incidentally by virtue of elevated serum calcium levels [44]. Patients with mild hyperparathyroidism also appear to be at no increased risk of osteoporosis or fractures [1], although vertebral fracture risk may be increased among more severely affected patients [45, 46]. A diagnosis of hyperparathyroidism was not associated with an increased risk of fracture in this study, but only 13 subjects were thought to have urolithiasis on this basis, which is consistent with other recent series [47, 48]. Much more common was a history of hyperuricemia or gout found in 146 patients. This is comparable to the proportion of patients with hyperuricosuria reported in clinical series [49, 50]. Among the latter patients, there was a reduction in the risk of limb fractures that was statistically significant after adjusting for gender and age that persisted in the multivariate analysis even after adjusting for body mass index.

Although not designed to evaluate pathogenetic mechanisms, this study provides the best empirical evidence to date that fracture risk is increased among patients with kidney stones. However, the increased risk is confined to vertebral fractures and is accounted for, in part, by the adverse influence of corticosteroid use. Low calcium intake could also be a risk factor, although we could not evaluate this possibility directly. Since low calcium intake is associated with an increased rather than decreased risk of kidney stones [51], it may be unwise to restrict dietary calcium among patients with urolithiasis, especially if the negative effects of corticosteroids on the skeleton are augmented by low calcium intake. More data are needed to resolve this issue. Excessive protein intake has also been associated with the development of stones [52] and with low bone mass [53], but we found little association of dietary protein intake with bone mineral density of the lumbar spine in a separate study of women from the general Rochester population [54]. It does seem clear that specific pharmacotherapy for urolithiasis is not responsible for the increased risk of vertebral fractures seen here, since pharmacotherapy was not an independent predictor in the analysis and because only a small minority of patients in this community-based cohort were so treated.

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REFERENCES

1. Khosla S, Melton LJ III: Secondary osteoporosis, in *Osteoporosis: Etiology, Diagnosis and Management* (2nd ed), edited by Riggs BL, Melton LJ III, Philadelphia, Lippincott-Raven Publishers, 1995, pp 183–204
2. Nilsson BE: Conditions contributing to fracture of the femoral neck. *Acta Chir Scand* 136:383–384, 1970
3. Williams HE, Prien EL Jr: Nephrolithiasis, in *Metabolic Bone Disease*, edited by Avioli LV, Krane SM, New York, Academic Press, 1977, pp 387–423
4. Pak CYC, Oata M, Lawrence EC, Snyder W: The hypercalciurias: Causes, parathyroid functions and diagnostic criteria. *J Clin Invest* 54:387–400, 1974
5. Strohmaier WL, Konakci H, Bichler K-H: Osteocalcin response to low calcium diet: A helpful tool for the differential therapy of hypercalciuria, in *Urolithiasis* (2nd ed), edited by Ryall R, Bais R, Marshall VR, Rofe AM, Smith LH, Walker VR, New York, Plenum Press, 1994, pp 627–629
6. Takeda M, Katayama Y, Tsutsui T, Komeyama T, Go H, Wakatsuki S, Sato S: Value of bone mineral analysis in patients with urolithiasis by single photon absorptiometry, dual photon absorptiometry, and dual energy x-ray absorptiometry–Comparison of primary hyperparathyroidism and idiopathic urolithiasis, and on the possibility of differentiating idiopathic hypercalciuria, in *Urolithiasis* (2nd ed), edited by Ryall R, Bais R, Marshall VR, Rofe AM, Smith LH, Walker VR, New York, Plenum Press, 1994, pp 609–611

7. Lawoyin S, Sismilich S, Browne R, Pak CYC: Bone mineral content in patients with calcium urolithiasis. *Metabolism* 28:1250–1254, 1979
8. Bataille P, Achard JM, Fournier A, Boudailliez B, Westeel PF, el Esper N, Bergot C, Jans I, Lalau JD, Petit J, Henon G, Laval Jeantet MA, Bouillon R, Sebert JL: Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. *Kidney Int* 39:1193–1205, 1991
9. Fournier A, Ghazali A, Bataille P, Cohen Solal M, Marie A, Brazier M, Sebert JL, Prin L: Bone involvement in idiopathic calcium-stone formers, in *Kidney Stones: Medical and Surgical Management*, edited by Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM, Philadelphia, Lippincott-Raven Publishers, 1996, pp 921–938
10. Fuss M, Pepersack T, Van Geel J, Corvilain J, Vandewalle J-C, Bergmann P, Simon J: Involvement of low-calcium diet in the reduced bone mineral content of idiopathic renal stone formers. *Calcif Tissue Int* 46:9–13, 1990
11. Jaeger P, Lippuner K, Casez J-P, Hess B, Ackermann D, Hug C: Low bone mass in idiopathic renal stone formers: Magnitude and significance. *J Bone Miner Res* 9:1525–1532, 1994
12. Kanis JA, Passmore R: Calcium supplementation of the diet. I: Not justified by present evidence. *Brit Med J* 298:137–140, 1989
13. Kanis JA, Passmore R: Calcium supplementation of the diet. II: Not justified by present evidence. *Brit Med J* 298:205–208, 1989
14. Nordin BEC, Heaney RP: Calcium supplementation of the diet: Justified by present evidence. *Brit Med J* 300:1056–1060, 1990
15. Cumming RG: Calcium intake and bone mass: A quantitative review of the evidence. *Calcif Tissue Int* 47:194–201, 1990
16. Parfitt AM: Chlorothiazide-induced hypercalcemia in juvenile osteoporosis and hyperparathyroidism. *N Engl J Med* 281:55–59, 1969
17. Goldsmith RS, Woodhouse CF, Ingbar SH, Segal D: Effect of phosphate supplements in patients with fractures. *Lancet* 1:687–690, 1967
18. Jones G, Nguyen T, Sambrook PN, Eisman JA: Thiazide diuretics and fractures: Can meta-analysis help? *J Bone Miner Res* 10:106–111, 1995
19. Kurland LT, Molgaard CA: The patient record in epidemiology. *Sci Am* 245:54–63, 1981
20. Melton LJ III: History of the Rochester Epidemiology Project. *Mayo Clin Proc* 71:266–274, 1996
21. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT: Renal stone epidemiology: A 25-year study in Rochester, Minnesota. *Kidney Int* 16:624–631, 1979
22. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ III: Incidence of clinically diagnosed vertebral fractures: A population-based study in Rochester. Minnesota, 1985–1989. *J Bone Miner Res* 7:221–227, 1992
23. Melton LJ III, Atkinson EJ, Madhok R: Downturn in hip fracture incidence. *Public Health Rep* 111:146–150, 1996
24. Owen RA, Melton LJ III, Johnson KA, Ilstrup DM, Riggs BL: Incidence of Colles' fracture in a North American community. *Am J Public Health* 72:605–607, 1982
25. Rose SH, Melton LJ III, Morrey BF, Ilstrup DM, Riggs BL: Epidemiologic features of humeral fractures. *Clin Orthop* 168:24–30, 1982
26. Melton LJ III, Sampson JM, Morrey BF, Ilstrup DM: Epidemiologic features of pelvic fractures. *Clin Orthop* 155:43–47, 1981
27. Cox DR: Some simple approximate tests for Poisson variates. *Biometrika* 40:354–360, 1953
28. Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481, 1958
29. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data*. New York, John Wiley and Sons, 1980, pp 1–321
30. Cox DR: Regression models and life-tables (with discussion). *J Royal Stat Soc* 34(Series B):187–220, 1972, 1972
31. Mallmin H, Ljunghall S, Persson I, Bergström R: Risk factors for fractures of the distal forearm: A population-based case-control study. *Osteoporosis Int* 4:298–304, 1994
32. Poór G, Atkinson EJ, O'Fallon WM, Melton LJ III: Predictors of hip fractures in elderly men. *J Bone Miner Res* 10:1900–1907, 1995
33. Seeman E, Melton LJ III, O'Fallon WM, Riggs BL: Risk factors for spinal osteoporosis in men. *Am J Med* 75:977–983, 1983
34. Lukert BP, Raisz LG: Glucocorticoid-induced osteoporosis: Pathogenesis and management. *Ann Intern Med* 112:352–364, 1990
35. Eastell R: Management of corticosteroid-induced osteoporosis. *J Intern Med* 237:439–447, 1995
36. Suzuki Y, Ichikawa Y, Saito E, Homma M: Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. *Metabolism* 32: 151–156, 1983
37. Lukert BP, Stanbury SW, Mawer EB: Vitamin D and intestinal transport of calcium: Effects of prednisolone. *Endocrinology* 93:718–22, 1973
38. Jaeger P, Hess B, Takkinen R, Zipperle L: Nutritional determinants of nephrolithiasis. *Adv Nephrol Necker Hosp* 24:217–225, 1995
39. Morris HA, Need AG, Horowitz M, O'Loughlin PD, Nordin BEC: Calcium absorption in normal and osteoporotic postmenopausal women. *Calcif Tissue Int* 49:240–243, 1991
40. Riggs BL, Kelly PJ, Kinney WR, Scholz DA, Bianco AJ Jr: Calcium deficiency and osteoporosis. Observations in one hundred and sixty-six patients and critical review of the literature. *J Bone Joint Surg* 49A:915–924, 1967
41. Gallagher JC, Riggs BL, Eisman J, Hamstra A, Arnaud SB, Deluca HF: Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients: Effect of age and dietary calcium. *J Clin Invest* 64:729–736, 1979
42. Francis RM, Peacock M, Taylor GA, Storer JH, Nordin BEC: Calcium malabsorption in elderly women with vertebral fractures: Evidence for resistance to the action of vitamin D metabolites on the bowel. *Clin Sci* 66:103–107, 1984
43. Riggs BL, Melton LJ III, O'Fallon WM: Drug therapy for vertebral fractures in osteoporosis: Evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. *Bone* 18(Suppl):197S—201S, 1996
44. Heath H III: Clinical spectrum of primary hyperparathyroidism: Evolution with changes in medical practice and technology. *J Bone Miner Res* 6(Suppl 2):S63–S70, 1991
45. Dauphine RT, Riggs BL, Scholz DA: Back pain and vertebral crush fractures: An unemphasized mode of presentation for primary hyperparathyroidism. *Ann Intern Med* 83:365–367, 1975
46. Kochersberger G, Buckley NJ, Leight GS, Martinez S, Studenski S, Vogler J, Lyles KW: What is the clinical significance of bone loss in primary hyperparathyroidism? *Arch Intern Med* 147:1951–1953, 1987
47. Fuss M, Pepersack T, Corvilain J, Vandewalle JC, Van Geertruyden J, Simon J, Kinnaert P: Infrequency of primary hyperparathyroidism in renal stone formers. *Br J Urol* 62:4–6 1988
48. Broadus AE: Primary hyperparathyroidism. *J Urol* 141:723–730, 1989
49. Coe FL: Treated and untreated recurrent calcium nephrolithiasis in patients with idiopathic hypercalciuria, hyperuricosuria, or no metabolic disorder. *Ann Intern Med* 87:404–410, 1977
50. Maschio G, Tessitore N, D'Angelo A, Fabris A, Pagano F, Tasca A, Graziani G, Aroldi A, Surian M, Colussi G, Mandressi A, Trinchieri A, Rocco F, Ponticelli C, Minetti L: Prevention of calcium nephrolithiasis with low-dose thiazide, amiloride and allopurinol. *Am J Med* 71:623–626, 1981
51. Curhan GC, Willett WC, Rimm EB, Stampfer MJ: A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 328:833–838, 1993
52. Goldfarb S: Dietary factors in the pathogenesis and prophylaxis of calcium nephrolithiasis. *Kidney Int* 34:544–555, 1988
53. Schaafsma G, van Beresteyn ECH, Raymakers JA, Duursma SA: Nutritional aspects of osteoporosis. *World Rev Nutr Diet* 49:121–159, 1987
54. Cooper C, Atkinson EJ, Hensrud DD, Wahner HW, O'Fallon WM, Riggs BL, Melton LJ III: Dietary protein intake and bone mass in women. *Calcif Tissue Int* 58:320–325, 1996