Urolithiasis in Tennessee: An Occupational Window into a Regional Problem

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ABSTRACT

Background: Urinary tract stones (stones) are believed to be unusually common in the southeastern United States but neither the incidence of nor the risk factors for stones are known.

Methods: In three well-defined occupational populations in eastern Tennessee, we assessed the prevalence, incidence, and cumulative incidence of stones and measured biochemical risk factors for lithogenesis.

Results: The age-adjusted prevalence of stones was 18.5 percent in Tennessee compared to 7.7 percent among White males in US NHANES (prevalence ratio 2.4, 95% CI 1.7, 3.3). The cumulative incidence (risk) was 27.8 percent by age 65, higher than in any other reported population. Risk factors were age, a family history, and urinary saturation with calcium-oxalate (COAX). Persons with a positive family history and the highest measured CAOX index had a predicted lifetime risk of 88.8 percent. Biochemical factors affecting lithogenesis were hypercalcuria, hyperoxaluria, and low urine volume.

Conclusion: Future research should characterize the geographic boundaries of a southeastern "stone-belt" and explore genetic and dietary hypotheses that might explain it. (*Am J Public Health* 1991;81:587–591)

Introduction

Kidney stones, an important source of morbidity, suffering, and medical expense, have received little epidemiologic attention. Three studies suggest an endemic area of stones in the Southeastern United States, but these rely upon hospital discharge data rather than incidence.[1–3] The absence of population-based incidence data in the US and the paucity of etiologic studies impede the identification of potentially modifiable risk factors such as diet and climate.[4,5]

The present study began as an investigation of reported urinary tract disorders among uranium workers in eastern Tennessee. Although no occupational association was found,[6] the study provided an opportunity to assess stone occurrence and risk factors for lithogenesis in a high-risk population. Our data support the concept of a regional "stone belt" and suggest clues as to its etiology.

Methods

Subjects

The uranium plant processed depleted and natural uranium and thorium from 1957 to 1970, and enriched uranium after 1970. Workers eligible for the study represent a gradient of exposure to unenriched uranium, compounds for which nephrotoxicity rather than radiation limits exposure.[7–9] The target population included: 1) highly exposed active, retired, and disabled production workers with 20 years employment before 1986; 2) a low exposure group of senior office and laboratory workers; 3) minimally exposed guards, ages 40–65, employed recently at the uranium plant; and 4) unexposed dairy workers from a nearby town. The dairy workers belong to the same trade union and local community. They produce tinned evaporated milk but have no special access to discounted milk or cheese that might affect stone risk.

Initially, a pilot questionnaire was administered to senior uranium workers and to guards. Later, a more extensive questionnaire and medical study were offered to the entire target population. Both questionnaires asked identical core questions about age and stones:

- "Have you ever had a kidney stone, including gravel in your urine?"
- "How many times have you had this?"
- "When did you first have this?"
- "Where were you treated?"

Workers interviewed in person were asked to sign a medical release form. The medical questionnaire also asked about a family history of stones, treatment for urinary tract infections, length of residence in the area, diabetes, hypertension, urinary instrumentation, prostatic disease, analgesics, smoking, "moonshine," and occupational exposure to heavy metals and solvents.

Data Collection

This activity included height, weight, seated blood pressure, serum for total calcium, phosphorus, uric acid and creatinine, sterile urine for quantitative urine culture and microscopy, and urine samples for chemistry, beta-2-microglobulin,

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TABLE 1—Participation in the Questionnaire and Medical Study

Employment Category	Number Eligible	Participation: Core Questionnaire N (%)	Participation: Full Medical Study (%)*
Uranium Exposed			
Active			
Hourly	58	58 (100)	50 (89)
Salaried	36	36 (100)	19 (59)
Retired			
Hourly	6	5 (83)	2 (40)
Salaried	10	10 (100)	2 (20)
Disabled	6	6 (100)	3 (50)
Referents			
Guards	43	43 (100)	10 (24)
Dairy Workers	51	50 (98)	37 (79)
Total	210	208 (99)	123 (62)

*Participation in medical study based upon the number (199 total) of workers present locally when testing performed.

retinol binding protein, and enzymes.[6] Urine was collected over 24 hours to measure the "stone risk profile," including eight promoters of lithogenesis (calcium, oxalate, sodium, uric acid, sulfate, phosphorus, and high or low pH), and three inhibitors (citrate, magnesium, and urine volume).[10,11] During collection, participants maintained their usual diet, fluid intake, and activity. Urine pH was measured immediately upon return of the sample; volume was determined by dilution of a known quantity of lithium. Aliquots were shipped in dry ice for analysis.[6]

Supersaturation with CAOX, dicalcium phosphate, monosodium urate, and urate was computed from measured values using a computer algorithm that considers the complex physiochemical interaction between multiple factors.[12] Supersaturation scores are expressed relative to the group mean of 176 persons without stones.[12]

Statistical Analyses

Age-specific prevalence reflects the number of workers ever having had a stone divided by the number in the corresponding age bracket, based upon age at interview. Age-adjusted prevalence was compared to White males in NHANES II[13] using maximum likelihood estimation.[14] Age-adjusted incidence reflects the age at first stone. Person years at risk (PYAR) were computed using life-table methods. Workers contribute PYAR from birth until they develop a stone or complete the interview, whichever is first. Age-adjusted incidence in Tennessee was compared to published data from the Mayo clinic,[5] using maximum likelihood estimation;[14] 95% confidence intervals used the test-based method.[14] Cumulative incidence (based on age at first stone) used the Kaplan-Meier method.[15] Factors associated with stones were identified using Student's t-test (for continuous variables) and Chi-square (for proportions). Associations were further tested using unconditional logistic regression. In this analysis, cases are persons ever reporting stones. Terms considered in the regression are age and all factors in Table 4 associated with stones at $p < 0.2$. The effect of each risk factor was assessed separately and in the presence of others. Age is retained in the final model because of the known association of stones and age. Other factors are retained if statistically significant ($p < 0.05$) or if inclusion of the factor substantially influences the coefficient for other terms. Second degree interaction was tested using stratified analyses; interaction terms are not included in the logistic model because none of these substantially modify the main effect terms.

Results

Table 1 shows participation rates by employment category. Overall, 208 eligible workers (99 percent) completed the core questionnaire. Of 199 present locally during the medical testing, 136 (68 percent) completed the medical questionnaire and 123 (62 percent) provided blood and 24-hour urine samples (full medical study). Participation was highest among active hourly workers released from duty for testing. Guards, retired, and salaried workers were either off-site, not released from duty, or had lower commitment to the study. All participants were male, 206 were White, with an average age of 52.1 and range of 38–72 years.

Medical Record Review

Forty of 208 workers reported stones (crude prevalence 19.2 percent). Of these, 37 were treated by civilian physicians, 30 (all those interviewed in person) provided medical release forms, 28 received records from the treating facility, and 25 had a stone confirmed. Stones could not be confirmed when the treating physician had retired or relocated. Confirmed stones accounted for 34 hospitalizations, 42 abdominal X-rays, five surgical extractions, and five lithotripsies. Chemical analyses of stones were recorded on 13 persons with recurrent stones; calcium oxalate was present in 12 (92 percent). Nineteen persons reported multiple stones; five of these had from five to 20, and one had 32.

Prevalence

Table 2 presents the prevalence of stones by age and occupational group. At all ages, the Tennessee workers reported more frequent stones than did White males in NHANES.[13] The age-adjusted prevalence in the Tennessee workers was 18.5 percent vs 7.7 percent in NHANES (prevalence ratio 2.4, 95% CI = 1.7, 3.3). Stone prevalence was similar in all occupational groups except guards. Prevalence in guards was 7 percent, significantly lower than that of other workers ($p = 0.02$) and similar to NHANES.[13]

Incidence and Cumulative Incidence

The age-adjusted incidence of first stones was 4.21 per 1,000 person-years, compared to 1.03 per 1,000 in Minnesota males[5] (RR = 4.1, 95% CI = 2.9, 6.0). The cumulative incidence (risk) of stone by age 60 was 23.7 percent, and by age 65 was 27.8 percent.

Characteristics Associated with Stones

Table 3 shows selected demographic and clinical attributes of persons with and without stones. Stone-formers in our study weighed more, used moonshine liquor less, reported a more frequent family history of stones and of male relatives treated for urinary infections, and were more likely to be treated for such infections themselves. Laboratory findings associated with stones are a significantly higher serum and urine calcium, and urinary supersaturation with CAOX and brushite. Findings not associated with stones in our study but of interest in the literature are serum and urine uric acid,[16] current cigarette smoking,* and analgesic use.[17]

Table 4 presents the results of unconditional logistic regression. The two factors most strongly associated with stones were the index for CAOX supersaturation in a current urine sample, and a family history of stones. The logistic model (Table 4) categorizes the CAOX index into tertiles. In Figure 1, the CAOX index is presented as a continuous variable. Figure 1 illustrates the probability of stones, as predicted by the model, in persons with and without a family history over the range of the CAOX observed in our study. Males with a family history and the highest measured CAOX index have a predicted lifetime probability of stones of 88.8 percent. Using multiple linear regression, we determined that the most important determinants of the CAOX were high urinary calcium and oxalate and low urine volume. Together, these terms explained 91.8 percent of the variance, with the individual contribution of calcium, urine volume, and oxalate being 49.5 percent, 34.1 percent, and 8.2 percent, respectively. Six other stone risk factors used to compute the CAOX index were statistically significant at the $p < 0.001$ level, but together these added only 6.7 percent to the explained variance.

TABLE 2—Age-Specific Prevalence of Stones: Tennessee Workers vs US

Age (years)	Tennessee (N = 208) N	Tennessee (N = 208) (%)	US NHANES[18] (N = 4331) N	US NHANES[18] (N = 4331) (%)
30–39	2	(20.0)	46	(5.0)
40–49	11	(13.3)	57	(7.4)
50–59	14	(21.2)	52	(7.9)
60–69	11	(23.9)	163	(9.2)
Age-adjusted	40	(18.5)	326	(7.7)

Occupation-Specific Prevalence of Stones: Tennessee Workers

Occupation	Potential Uranium Exposure	Workers N	Prevalence Stones N	Prevalence Stones (%)
Uranium workers				
Production	(High)	95	19	(20)
Office	(Low)	20	5	(25)
Guards	(Low)	43	3	(7)
Dairy workers	(None)	50	13	(26)
Total		208	40	(19)

Discussion

Our principal finding is an increased risk of stones among males in eastern Tennessee, consistent with previous reports of a regional "stone belt."[1–3] At highest risk are persons with a positive family history whose urine is supersaturated with CAOX, a major ingredient of most stones.[4] Provided that our findings reflect regional occurrence, they suggest that stones are an important public health problem in the southeast, and provide some clues about etiology.

The lifetime risk of stones among the Tennessee workers is higher than in any other reported population. Risk by age 60 is 24 percent in our study, compared to 5 percent in Minnesota,[5] 7 percent in northern California,[4] and 19 percent in Uppsala, Sweden.[18] These regional differences are larger than can be explained by differences in the methods for estimating risk. The Swedish data, for example,[18] are based upon a prevalence survey of renal colic in 1781 men, age 60. The US NHANES survey,[13] using similar methods but inquiring about stones instead of renal colic, show a lifetime prevalence of 9.2 percent in White males ages 60–69. The lower risks observed in the California and Minnesota studies are based upon incidence rates of physician visits.[4,5] Incidence is converted to risk using the formula [$\text{risk} = 1 - e^{(-\text{Incidence} \times \text{Time})}$].

Several findings suggest that the risk of stones in our study is regional rather than occupational. First, a family history of stones affecting first degree relatives who have never worked at either plant was common in both stone-formers (52 percent) and those without stones (21.5 percent). This can be compared to Sweden, where 29.4 percent of stone-formers and 15.3 percent of nonstone-formers report a family history.[18] Second, the occurrence of stones in the uranium workers bears no relation to the intensity or duration of occupational exposure. Stones are slightly less common in workers with direct exposure to uranium and thorium than in unexposed workers. Third, stone occurrence is similar in the uranium and dairy workers. If stone occurrence were due to occupation it would be unlikely that two such different occupational settings would cause a nearly identical effect.

The geographic boundaries of the so-called "stone-belt" are poorly defined. Four southeastern states (North Carolina, South Carolina, Virginia, and Tennessee) rank high in terms of hospitalizations for stones as a proportion of all hospital admissions.[1] There are limitations to these hospital discharge data, however,[4,5] and no studies have collected population-based data on incidence in the southeast US. Such data would be extremely useful in mapping the occurrence of stones, defining high-risk areas, and identifying preventable risk factors.

No cause has yet been identified for increased stone-formation in the southeast. Various hypotheses include water softness,[19] sunlight and heat,[20] dietary consumption of meat,[16] and carbonated beverages.[21] All of these hypotheses are based upon ecological evidence and have not been tested in studies assessing both stone occurrence and the exposure of individuals to the proposed risk factors. Our study is the first to measure biochemical risk factors in urine in a high-risk population; as such it helps to narrow the range of hypotheses to be pursued in future research. The single most important factor contributing to CAOX supersaturation in our study was increased urinary calcium.

Twenty-five (20.7 percent) of participants in the medical study had clinical hypercalcuria (>300 mg per 24 hours).[16] We did not obtain a dietary history and cannot assess whether the increased uri-

*Fitzsimmons SC: Self-reported kidney stone disease among Black and White adults: Prevalence and correlates in NHANES 11 (1976–1980). Presentation at 116th annual meeting of the American Public Health Association, Nov. 15, 1988, Boston.

TABLE 3—Demographic and Clinical Characteristics of Persons with and without Stones

	Stones			No Stones			
Characteristic	Mean	(SD)	Range	Mean	(SD)	Range	p value⁺
Age years*	53.5	(8.5)	38–71	51.7	(7.9)	38–72	—
Weight kg.**	92.8	(15.5)	69–135	85.4	(13.0)	56–120	(0.01)
% Born locally**	86.2			85.2			—
% Away ≥ 20 years**	9.7			19.4			(0.2)
% Ever use moonshine liquor**	25.9			61.5			(0.001)
% Family history of stones**	51.7			21.5			(0.001)
% Family history of infection**	20.7			5.7			(0.02)
% Personal history of infection**	41.1			21.5			(0.009)
% Smoking, current**	34.5			35.5			—
% Phenacetin usage**	0.0			7.2			—
Calcium, serum (mg/dl)***	9.8	(1.0)	9.3–10.6	9.6	(1.0)	9.2–10.6	(0.006)
Calcium urine (mg/dl)***	13.2	(2.2)	2.8–44.7	7.8	(1.9)	2.4–42.6	(0.001)
Calcium urine (mg/day)***	250	(1.5)	98–455	164	(2.0)	9–850	(0.0001)
Oxalate, urine (mg/day)***	47.6	(1.3)	29–74	41.2	(1.4)	13–83	(0.051)
Uric acid serum (mg/dl)***	6.3	(1.2)	4.2–8.9	6.5	(1.3)	3.5–9.8	—
Uric acid urine (mg/day)***	517	(1.8)	149–1434	504	(1.6)	125–1423	—
Urine volume (L/day)***	1.6	(1.4)	0.8–2.8	1.7	(1.6)	0.4–3.9	—
Calcium-oxalate index***	2.4	(1.7)	0.5–6.2	1.5	(1.8)	0.1–4.2	(0.0009)
Brushite index***	2.3	(2.4)	0.2–7.0	1.4	(2.7)	0.02–7.1	(0.048)

*Data on 208 persons completing core questionnaire.
**Data on 136 participants completing medical questionnaire.
***Geometric mean for 123 subjects providing blood and 24-hour urine.
⁺P-value stated only if p ≤ 0.20.

TABLE 4—Logistic Regression: Factors Predicting Kidney Stones*

Risk Factors	Odds Ratio	SE	(95% CI)
Univariate Analyses			
Calcium-Oxalate Saturation Index			
Second tertile*	4.62	0.782	(1.0, 21.4)
Third tertile*	6.20	0.760	(1.4, 27.5)
Family history of stones	3.30	0.410	(1.5, 7.4)
Family history of infection	2.64	0.503	(1.0, 7.1)
Age 50–59 years	1.12	0.493	(0.4, 2.9)
Age ≥ 60 years	1.65	0.493	(0.6, 4.3)
Multivariate Analyses			
Calcium Oxalate Saturation Index			
Second tertile*	3.79	0.803	(0.8, 17.8)
Third tertile*	5.91	0.765	(1.3, 26.5)
Family History of Stones	3.51	0.425	(1.5, 8.1)
Age 50–59 years	1.62	0.505	(0.6, 4.4)
Age ≥ 60 years	2.21	0.505	(0.8, 5.9)

*Analysis based on 123 persons submitting blood and 24-hour urine sample.
**Mean scores for calcium-oxalate tertiles are 0.90, 1.79 and 3.01 for first, second, and third tertiles. Index is defined in text.

nary calcium was due to diet (milk, cheese, and meat) or to increased gastrointestinal absorption. However, we can exclude drinking water as a major source of calcium because municipal water supplies in the area have been monitored since 1982 and have unusually soft water due to low calcium.[22] Similarly, sunlight and its effect upon vitamin D cannot explain the measured values in our study, because the study was conducted in January. A second important determinant of CAOX was low urine volume. This cannot be attributed to incomplete urine collection, because it occurred in the presence of high 24-hour excretion of other stone risk factors. Low fluid intake is the most likely explanation for reduced urine volume and increased concentration. It is unclear why fluid intake should be low in these workers, although prohibition against alcoholic beverages in many areas of the southeast may play some role. Alcohol exerts a diuretic effect by suppressing the release of anti-diuretic hormone.[23] Consumption of moonshine liquor is negatively associated with stones in our study. The hypothesis that alcohol may protect against stones is plausible and deserves further evaluation.

Mildly elevated urinary oxalate (55–100 mg/24 hours)[24] occurred in 20 (16.5 percent) of the workers in our study. These levels are below those found in primary hyperoxaluria,[24] but may be consistent with dietary exposure. Foods commonly eaten in the southeast include several sources of oxalate (collards, mustard greens, kale, and ice tea).[25] Oxalate excretion contributed relatively little to urinary saturation with CAOX compared to hypercalcuria and low urine volume. However, the presence of oxalates in typical southern cuisine provides an intriguing hypothesis to be tested in future studies.

We cannot explain the low frequency of stones among the guards in our study. Guards were culturally different from the other workers. Twenty guards (46.5 percent) vs 10 (7.9 percent) of the other workers were retired military servicemen who had spent 20 or more years away from the area ($p < .0001$). Too few guards participated in the medical study to allow us to examine whether differences existed in their urine composition. The low participation occurred largely because guards

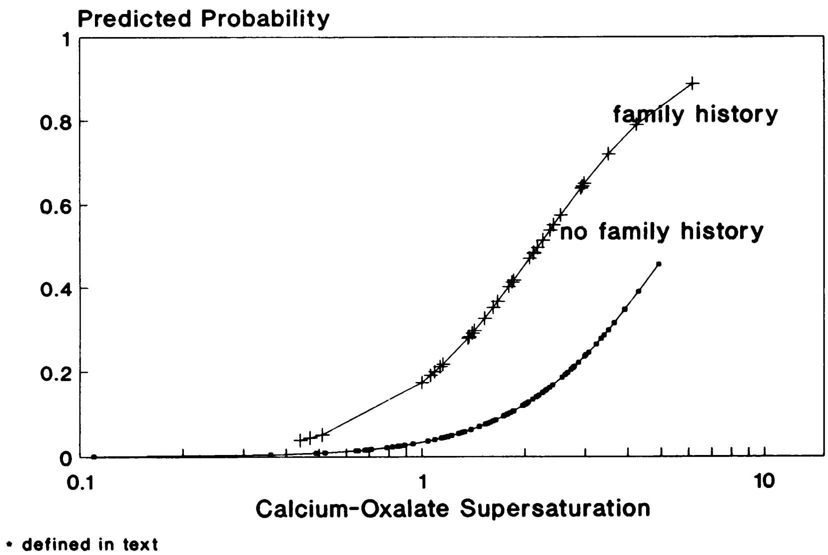

FIGURE 1—Probability of Stones by Family History and Calcium-Oxalate Supersaturation Index*

could not be released from duty to participate during working hours.

A limitation of our study is that the assessment of risk factors for stone-formation in urine is based upon a single 24-hour sample, obtained some years after the actual passing of stones. It is likely that excretion of most of these substances varies over time. Nevertheless, the strong association between current CAOX excretion and lifetime stone occurrence is consistent with the known importance of calcium and oxalate in stone formation. Excretion appears to be sufficiently stable to reflect a gradient of risk as current concentration increases. In summary, the study found an increased risk of urolithiasis and risk factors related to stone formation in male workers in eastern Tennessee. Future research should define the geographic range of increased kidney stone formation in the southeast and identify its causes. □

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