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Relationship between Urinary Calcium and Bone Mineral Density in Patients with Calcium Nephrolithiasis

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Abstract

Purpose—Calcium nephrolithiasis is associated with an increased risk of osteoporosis and fracture. Hypercalciuria has been assumed to be pathogenic for bone loss in kidney stone formers, although this association was shown in small crosssectional studies. We explored the association of urine calcium with bone mineral density in kidney stone formers.

Materials and Methods—We retrospectively studied bone mineral density in kidney stone formers. Excluded were subjects with hypercalcemia, chronic bowel disease, primary hyperparathyroidism, distal renal tubular acidosis or endogenous creatinine clearance less than 40 ml per minute. We included 250 males and 182 females subdivided into 145 who were estrogen treated and postmenopausal, and 37 who were nonestrogen treated and postmenopausal. We assessed the association of lumbar spine and femoral neck bone mineral density with 24-hour urine calcium on random and restricted diets, and while fasting using univariable and multivariable models adjusting for body mass index, urine sodium and sulfate.

Results—On multivariable analysis no significant association was found between urine calcium on a random or a restricted diet, or during fasting conditions and femoral neck or lumbar spine bone mineral density in men and estrogen treated women. In estrogen untreated women lumbar spine bone mineral density inversely correlated with urine calcium on the restricted diet ($r = -0.38$, $p = 0.04$ and adjusted $r = -0.45$, $p = 0.02$) and in the fasting state ($r = -0.42$, $p = 0.05$).

Conclusions—Unlike in previous small cross-sectional studies we found no significant relationship between urine calcium and bone mineral density in a large group of calcium kidney stone formers. However, a significant inverse relationship was found in estrogen untreated kidney stone formers only. This study suggests that mechanism(s) other than hypercalciuria explain the

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lower bone mineral density and the higher fracture risk in patients who are kidney stone formers. It also highlights the role of estrogen on bone integrity.

Keywords

kidney calculi; estrogens; urine; calcium; bone density

Nephrolithiasis is a major health and economic burden in the United States and worldwide.¹ Several population based epidemiological studies have established a high prevalence of both axial and appendicular skeletal fractures among kidney stone formers.^{2,3} However, in a recent large cohort of 9,856 postmenopausal women stone formation was not associated with either BMD or skeletal fractures after adjusting for covariates that are associated with both osteoporosis and kidney stones.⁴ Major limitations of some of these population based cohort studies have been the reliance on self-report of stone incidence, lack of availability of stone composition, dietary composition, fluid intake, calcium and vitamin D supplementations, drugs known to influence the risk of kidney stone disease and most importantly urinary biochemical profiles.⁵⁻⁷

Furthermore, most of these population based studies did not adjust for covariates influencing the development of osteoporosis such as ethnicity, general health and use of bone protective agents.^{2,3} Nevertheless, hypercalciuria and a negative calcium balance, which are common in patients with idiopathic hypercalciuria,⁸ have been assumed to be pathogenic for bone loss in kidney stone formers. This association was shown in several cross-sectional studies in a small number of kidney stone formers.⁹⁻¹¹

We performed a multivariable analysis including urinary sodium and sulfate as surrogate markers for salt and animal protein intake, respectively, which have both been shown to increase urinary calcium excretion⁵ and increase the risk of bone disease.¹¹ We also included BMI in the multivariable analysis due to its positive correlation with BMD.¹²

To date the underlying pathophysiological mechanisms of bone loss and higher fracture risk in stone formers has not been fully elucidated. In view of the limitations of past studies we examined the relationship between urinary calcium excretion and BMD in a larger population of male and female untreated kidney stone formers on a random diet, those following a restricted dietary regimen limiting salt intake and those in the fasting state to cover all physiological states of urinary calcium excretion.

MATERIALS AND METHODS

Study Participants

The data on calcium stone forming subjects were obtained retrospectively from the Kidney Stone Registry at our institution between 1980 and 2015. Included in study were subjects 21 years old or older with calcium nephrolithiasis who underwent BMD measurement. Excluded were individuals with creatinine clearance less than 40 ml per minute, renal tubular acidosis, chronic diarrhea, primary hyperparathyroidism, chronic urinary tract infection, uric acid stone formers, cystinuria, patients taking any anti-osteoporotic medication, calcium and vitamin D supplements, and patients in poor general health. A total

of 3,390 patient records were screened. Based on these criteria data were obtained on 432 patients (250 males and 182 females) who were evaluated in our clinic.

Of the 182 female subjects 80 were considered postmenopausal due to natural cessation of menses or to surgical intervention. Of the 80 postmenopausal women 43 were on HRT at the time of evaluation. Postmenopausal women not on HRT were classified as nonestrogen exposed whereas premenopausal women and postmenopausal women taking HRT were classified as estrogen exposed. Subject data were obtained at the initial stone visit in which participants were instructed to hold all medications known to influence urinary kidney stone profiles, such as alkali treatment and thiazide diuretics, for 1 week prior to the clinic visit.

This study was approved by the institutional review board at University of Texas Southwestern Medical Center at Dallas and all participants provided written informed consent.

Data Collection and Measurements

Initial stone visits typically included 2, 24-hour urine samples obtained while the subjects were maintained on an ad lib diet (random 24-hour urine). For data analysis purposes the 2, 24-hour urine samples were averaged. Following the initial visit a single 24-hour urine sample was obtained while following a low sodium diet (approximately 100 mEq sodium per day) for 7 days (restricted urine). All 24-hour urine samples were analyzed for total volume, creatinine, calcium, sodium and SO_4 .

A fasting 2-hour urine sample was obtained after the patients fasted overnight for total volume, calcium and creatinine (fasting urine). At the end of the 2-hour fasting collection a venous serum sample was obtained for calcium and creatinine.

Postmenopausal status was defined as participants who had lacked a menstrual cycle in the past 12 months due to natural or surgical causes after excluding other causes of menstrual cycle cessation, such as pregnancy, breastfeeding and other medical conditions/treatments. HRT was defined as the current use of estrogen or an estrogen containing agent, such as estrogen pills/combination pills or estrogen patches/combination patches.

Analytical Procedures

BMD was measured by trained certified DXA technologists. The LS and FN were measured either by dual photon absorptiometry (Lunar Radiation, Madison, Wisconsin) or by DXA (Hologic, Bedford, Massachusetts). At the time of conversion from dual photon absorptiometry to DXA the instruments were cross calibrated. To account for differences in instruments Z-scores are reported. The instruments were calibrated daily using a phantom for the lumbar spine. Yearly precision measurements were performed as recommended by ISCD (International Society for Clinical Densitometry).

Urine calcium was measured by atomic absorption spectroscopy while urine creatinine was measured using the picric acid method. Urinary sodium was analyzed by flame photometry and urinary SO_4 was measured by ion chromatography.

Statistical Analyses

Results are presented as the mean $\pm$ SD unless otherwise specified. The relationship between bone mineral density and urinary calcium variables were analyzed with the Spearman correlation coefficient. The Spearman partial correlation was used to adjust for BMI, urine sodium and urine sulfate. Two-sided $p < 0.05$ was considered statistically significant. In females the interaction between estrogen status and urinary calcium was assessed by linear regression analysis using log transformed urinary calcium. Statistical analysis was performed with SAS®, version 9.4.

RESULTS

Kidney Stone Former Characteristics

The demographic and biochemical characteristics of stone formers who did vs did not undergo DXA testing were similar in our stone registry. A total of 250 males and 182 females were included in analysis. Race and ethnic distribution was similar in males and females (table 1). In the male cohort mean age was 48 ± 13 years and mean BMI was 29.0 ± 5.3 kg/m². Mean age in the estrogen treated and estrogen untreated cohorts was 41 ± 10 and 57 ± 10 years, and mean BMI was 26.8 ± 5.9 and 28.9 ± 6.1 kg/m², respectively.

In the male cohort the mean LS Z-score was -0.3 ± 1.6 and the mean FN Z-score was -0.2 ± 1.0 . In females the estrogen treated and estrogen untreated cohorts had a mean LS Z-score of -0.2 ± 1.1 and 0.0 ± 1.8 , and a mean FN Z-score of -0.2 ± 1.0 and -0.2 ± 1.0 , respectively. Of calcium stone formers 14% of males, 11% of estrogen treated females and 14% of estrogen untreated females had a Z-score of less than -2.0 , which is below the expected range for age and gender. Of calcium stone formers 58% of males, 40% of estrogen treated females and 62% of estrogen untreated females were considered hypercalciuric on a random diet with urinary calcium greater than 250 mg/day or on a restricted diet with urinary calcium greater than 200 mg per day.

Bone Mineral Density Z-Score Relationship to Urinary Calcium

Male Cohort—On the univariable (unadjusted) and multivariable (adjusted) analyses in the male cohort 24-hour urinary calcium while on the random and restricted diets showed no relationship with LS Z-scores (table 2 and supplementary figure, <http://jurology.com/>). There was also no relationship of either model between fasting Ca/Cr and lumbar spine Z-scores.

For the FN Z-scores the only significant relationship was with random diet 24-hour urinary calcium in the univariable model. This relationship was not found after multivariable adjustment, that is after adjusting for BMI, urine sodium and urine sulfate. The unadjusted and adjusted relationships between 24-hour urinary calcium on a restricted diet were nonsignificant after multivariable adjustment.

Female Cohorts—On regression analysis of urine calcium on the LS Z-score a significant interaction between estrogen status and urine calcium on the random and restricted diets was

observed. This indicated different slopes between estrogen treated and estrogen untreated females (see figure).

In the estrogen treated cohort no significant relationship was found between 24-hour urinary calcium and the random or the restricted diet, or the LS Z-score in the unadjusted or adjusted models (table 3). Similarly, fasting Ca/Cr showed no significant relationship with the LS Z-score whether adjusted or unadjusted. However, in the estrogen treated group 24-hour urinary calcium on the random or restricted diet showed significant relationships with the FN Z-score in the unadjusted model.

These associations were nonsignificant in the adjusted model. In the estrogen untreated cohort a significant relationship was found between 24-hour restricted diet calcium and the LS Z-score (see figure). The significance of this relationship persisted after adjusting for confounding variables, including BMI, sodium and sulfate. Fasting Ca/Cr vs the LS Z-score was significant in the unadjusted model but nonsignificant in the adjusted model ($p = 0.07$). No significant relationships were detected between urinary calcium and FN Z-scores in the estrogen untreated cohort.

In all multivariable models examined BMI was the strongest covariate accounting for the association of urine calcium with BMD.

DISCUSSION

To our knowledge this is the first study to examine the association of urinary calcium and BMD in a large number of calcium stone formers while accounting for gender, menopausal state and estrogen status. Following multiple adjustments we found no significant association between urinary calcium and BMD at either the LS or the FN in men or in estrogen treated women (tables 1 and 2).

Estrogen deficiency inhibits intestinal calcium absorption and directly enhances bone resorption.¹³ These effects may be accentuated when dietary calcium intake is restricted. In nonestrogen treated postmenopausal women there was a significant inverse association between urinary calcium and BMD at the LS. The association between 24-hour urinary calcium on a restricted diet and the LS BMD was statistically significant ($p = 0.02$). However, this relationship was not significant on random diet 24-hour urinary calcium ($p = 0.09$) or fasting urinary calcium ($p = 0.07$, table 2).

The finding in the LS was expected since estrogen deficiency is known to mainly affect trabecular-rich bone, which is the main constituent of the vertebral spine. This observation suggests that increased bone resorption may account for such a relationship in this subset of females with kidney stones.

Our data contrast with findings in several previous cross-sectional studies in which an association between urinary calcium and BMD was observed in kidney stone formers.^{11,14-17} The explanation for the differences between those studies and our current data might be driven by sample size, by the inclusion of both genders and estrogen status, and also by publications prior to the adoption of T-scores and Z-scores by WHO.^{14,15,17-19}

However, our data are consistent with a recent analysis of 1,500 elderly men in MrOS (Osteoporosis fractures in Men), which showed a lack of relationship between hypercalciuria and osteoporosis.²⁰ In that cohort men with osteoporosis more often had a history of fractures or kidney stones. However, among more than 300 men with both BMD and 24-hour urine calcium no relationship was found between urinary calcium and osteoporosis. The results of our study suggest that urinary calcium may be a marker but not a cause of bone loss in this population, as previously conceived.^{14,15,17–19}

The mechanism(s) by which bone loss develops in patients with kidney stones is yet to be fully explained. Osteoporosis is a heterogeneous and complex bone disorder characterized by an imbalance in bone resorption and bone formation as well as deterioration of the microarchitectural integrity of bone. Bone histomorphometric analyses performed in kidney stone formers have shown impaired bone formation as a characteristic finding.^{21,22} This would not be the expected finding if hypercalciuria alone has a sole pathogenetic role in the development of bone loss in this population.

Idiopathic hypercalciuria is a heterogeneous disorder which could result from increased synthesis of calcitriol or increased sensitivity to calcitriol, up-regulating its own receptor but influencing the target organs differently. There is evidence of increased intestinal absorption of calcium in this population.^{23,24} In vitro organ culture incorporating ³H-proline into collagenase digested protein in fetal rat calvaria showed an inhibitory role of calcitriol in collagen synthesis as well as in osteoblastic cell proliferation.²⁵ The inhibitory levels of calcitriol was shown to be exerted at 10⁻¹⁰ M, which is not different from the level of these vitamin D metabolites attained in hypercalciuric stone formers.^{26–28}

These results are in line with our previous study in a group of healthy eugonadal men with idiopathic osteoporosis who had impaired bone formation concomitant with calcitriol levels and hypercalciuria.²⁹ In these subjects hypercalciuria did not appear to be due to increased skeletal calcium loss but rather related to enhanced intestinal calcium absorption caused by increased calcitriol levels. This phenotype is similar to that of hypercalciuric kidney stone formers.

The novelty of the current study is its investigation of a substantial number of kidney stone formers, considering different gender groups, menopausal status and use of estrogen. However, there are certain limitations as well. The observational design limited an understanding of the causality in relationships. We could not present fracture data but bone density has been used as a proxy for bone strength and in a large number of studies it has been shown to be a predictor of fracture risk.³⁰ An additional limitation is the lack of data on dietary calcium intake and calciotropic hormones. Finally, the small sample size of the estrogen untreated group may have reduced the power to detect significant relationships between BMD and urine calcium excretion.

CONCLUSIONS

The results of this study suggest that urinary calcium may be only a marker of but not pathogenetic for the development of bone loss in this population. Future investigations must

be directed toward understanding whether the coexistence of hypercalciuria in this population augments bone formation defects.

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Abbreviations and Acronyms

BMD	bone mineral density
BMI	body mass index
Ca/Cr	calcium-to-creatinine ratio
DXA	dual energy x-ray absorptiometry
FN	femoral neck
HRT	hormone replacement therapy
LS	lumbar spine

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Regression analysis in female cohorts revealed significant interactions between estrogen status and urinary calcium (Ca) for random ($p = 0.01$) and restricted ($p < 0.001$) diet calcium but not for fasting Ca/Cr ($p = 0.30$).

Table 1

Study cohort demographics, bone mineral density and urinary parameters

	Male	Female	
		Estrogen	No Estrogen
No. pts	250	145	37
No. race:			
Native American	2	1	0
Asian	8	3	0
African American	6	3	0
Hispanic	11	6	1
Caucasian	223	132	36
Mean $\pm$ SD age	48.3 $\pm$ 12.7	41.1 $\pm$ 10.2	56.7 $\pm$ 10.2
Mean $\pm$ SD BMI (kg/m ²)	29.0 $\pm$ 5.3	26.8 $\pm$ 5.9	28.9 $\pm$ 6.1
Mean $\pm$ SD Z-score:			
Lumbar spine	-0.3 $\pm$ 1.6	-0.2 $\pm$ 1.1	0.0 $\pm$ 1.8
Femoral neck	-0.2 $\pm$ 1.1	-0.2 $\pm$ 1.0	-0.2 $\pm$ 1.0
Mean $\pm$ SD fasting urinary Ca/Cr (mg/mg)	0.08 $\pm$ 0.04	0.09 $\pm$ 0.05	0.12 $\pm$ 0.05
Mean $\pm$ SD random diet urinary values:			
Calcium (mg/day)	269 $\pm$ 124	225 $\pm$ 118	245 $\pm$ 124
Sodium (mEq/day)	209 $\pm$ 81	157 $\pm$ 62	151 $\pm$ 70
SO ₄ (mEq/day)	43.2 $\pm$ 15.8	32.6 $\pm$ 15.6	31.7 $\pm$ 13.0
Mean $\pm$ SD restricted diet urinary values:			
Calcium (mg/day)	200 $\pm$ 105	167 $\pm$ 83	209 $\pm$ 93
Sodium (mEq/day)	132 $\pm$ 75	104 $\pm$ 53	109 $\pm$ 59
SO ₄ (mEq/day)	43.6 $\pm$ 18.3	31.7 $\pm$ 14.8	32.1 $\pm$ 15.5

Table 2

Correlations between urinary calcium and bone mineral density in male calcium stone formers during random and restricted diets, and fasting

Z-Score	No. Pts	Unadjusted (Spearman test)		Adjusted*	
		ρ	p Value	Partial ρ	p Value
L2-L4:					
Random urine calcium	246	0.02	0.74	-0.09	0.17
Restricted urine calcium	222	0.02	0.76	-0.08	0.26
Fasting Ca/Cr [†]	215	-0.01	0.86	-0.03	0.71
Femoral neck:					
Random urine calcium	245	0.20	0.002	0.03	0.66
Restricted urine calcium	223	0.13	0.06	0.01	0.87
Fasting Ca/Cr [†]	215	0.02	0.80	0.002	0.98

* Random 24-hour and restricted urinary calcium regression adjusted for BMI, and urinary sodium and SO₄.

[†] Adjusted for BMI.

Table 3

Correlations between urinary calcium and bone mineral density in female calcium stone formers by menopausal status and estrogen use during random and restricted diets, and fasting

Z-Score	No. Pts	Estrogen		Partial ρ	p Value	Estrogen Adjusted [†]
		Unadjusted [*]	ρ			
<i>Estrogen</i>						
L2-L4:						
Random urine calcium	139	0.05	0.59	-0.12	0.16	
Restricted urine calcium	121	0.10	0.29	-0.02	0.82	
Fasting Ca/Cr	117	0.02	0.84	0.02	0.83	
Femoral neck:						
Random urine calcium	141	0.27	0.001	0.13	0.13	
Restricted urine calcium	123	0.25	0.006	0.09	0.31	
Fasting Ca/Cr	118	0.01	0.90	0.02	0.82	
<i>No estrogen</i>						
L2-L4:						
Random urine calcium	34	-0.17	0.34	-0.31	0.09	
Restricted urine calcium	29	-0.38	0.04	-0.45	0.02	
Fasting Ca/Cr	22	-0.42	0.05	-0.40	0.07	
Femoral neck:						
Random urine calcium	35	0.01	0.96	-0.08	0.67	
Restricted urine calcium	30	-0.04	0.83	-0.21	0.29	
Fasting Ca/Cr	23	-0.27	0.21	-0.32	0.15	

^{*} Spearman test.

[†] Random and restricted 24-hour urinary calcium regressions adjusted for BMI, sodium and SO₄, and fasting urinary Ca/Cr correlations adjusted for BMI.