The importance of urinary calcium in postmenopausal women with osteoporotic fracture

Miguel Angel Ochoa-Hortal Rull, MD;[*] MD, María del Carmen Cano-García, MD;[†] Miguel Arrabal-Martín, PhD;[§] Miguel Angel Arrabal-Polo, PhD[†]

[*]Trauma Department, Hospital Rafael Mendez, Lorca, Murcia, Spain; [†]Urology Department, Hospital La Inmaculada, Huercal-Overa, Spain; [§]Urology Department, Complejo Hospitalario Universitario Granada, Instituto IBS Granada, Granada, Spain

Cite as: *Can Urol Assoc J* 2015;9(3-4):E183-6. http://dx.doi.org/10.5489/cuaj.2695
Published online April 13, 2015.

Abstract

Introduction: Calcium stones are associated with osteoporosis and manifested mainly by elevated fasting urinary calcium/creatinine ratio. The objective of this study is to demonstrate the presence of abnormal metabolism of calcium and calciuria in women with osteoporotic fracture with no previously known renal lithiasis compared to women without osteoporosis and without renal lithiasis.
Methods: In total, 87 women were included in the study. They were divided into two groups: Group 1 with 55 postmenopausal women with osteoporotic fracture and without renal lithiasis; and Group 2 with 32 postmenopausal women without osteoporosis and without history of renal lithiasis. The following parameters of phospho-calcium metabolism were analyzed: calciuria 24-hour, oxaluria 24-hour, uricosuria 24-hour, and citraturia 24-hour. The presence of hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia was compared between groups. Statistical significance was set at $p \leq 0.05$.
Results: The mean age was 70.1 ± 13.8 in Group 1 and 56.7 ± 6.4 in Group 2 ($p = 0.0001$). Women in Group 1 had higher levels of serum alkaline phosphatase ($p < 0.05$) and fasting urinary calcium/creatinine ratio ($p < 0.05$). The percentage of patients with hypercalciuria in Group 1 (40%) was higher compared to Group 2 (18.8%) and statistically significant ($p = 0.04$). There were no statistically significant differences in the percentage of hyperoxaluria, hyperuricosuria, and hypocitraturia between groups. This study has its limitations including its cross-sectional nature at a unique centre and its low number of patients.
Conclusion: The determination of urinary calcium and fasting calcium/creatinine ratio in postmenopausal women with osteoporotic fracture without renal lithiasis may facilitate individualization of medical therapy and decreasing lithogenic risk.

Introduction

Patients with recurrent calcium stones have a greater percentage of bone mineral density loss,[1] manifested primarily by increased fasting urinary calcium levels,[2] which is also a determinant of osteopenia.[3] Just as calcium nephrolithiasis is associated with osteoporosis,[4] osteoporosis is an independent risk factor for producing symptomatic nephrolithiasis.[5] Therefore, there is a connection between the two conditions, evidenced primarily by alterations in urinary calcium. Although the pathophysiology of bone mineral density loss in patients with stone disease is unclear and the cause-effect relationship between the two conditions has not been established, we know that immunological, inflammatory, hormonal and dietary factors significantly influence the occurrence of the two phenomena.[6] In women with calcium stones, higher fasting urinary calcium levels have been observed with greater bone mineral density loss and elevated markers of bone turnover, establishing a positive linear relationship between markers of bone resorption and urinary calcium.[7]

Moreover, it has been observed that even in patients without stones, bone health is related to the presence or absence of idiopathic hypercalciuria; this underscores the importance of monitoring bone metabolism.[8] Calcium stones and osteoporosis are common pathologies, especially after the fourth or fifth decade of life,[1] and the relationship between them has been previously recognized.[1-3] However, in patients with osteoporotic fracture who have yet to develop stones, it may be important to measure their urine calcium levels to tailor a more individualized medical treatment and to reduce the risk of nephrolithiasis if they have hypercalciuria.

The aim of our present study is to analyze calcium metabolism and calciuria in postmenopausal women with osteoporotic fracture and without renal stones compared to women without osteoporosis and without renal stones.

Methods

From January 2013 to June 2014, 87 women were included in this study and divided into two groups: Group 1 with 55 postmenopausal women with osteoporotic fracture; and Group 2 with 32 postmenopausal women without osteoporosis.

Prior to classifying patients in the study, bone mineral densitometry was obtained using dual energy X-ray absorptiometry for diagnosing osteoporosis (T-score ≤-2.5) or absence of osteoporosis (T-score >-2.5).

Patients in Group 1 were from the Trauma Department where they underwent surgery after suffering an osteoporotic fracture in the following locations: hip (60%), wrist (32%), spine (2.5%), and other locations (5.5%). Patients in Group 2 were from the Department of Urology. They were treated for urologic pathologies (not for lithiasis) and did not have osteoporosis.

Group 1 included postmenopausal women with osteoporotic fracture based on the location of the fracture, fracture mechanism and the presence of osteoporosis by bone densitometry. Group 2 included postmenopausal women without osteoporosis determined by bone densitometry.

We excluded men, patients with a history of kidney stones, bone disease or renal chronic insufficiency, patients undergoing treatment with vitamin D, calcium, antiresorptive drugs, corticosteroids, thiazides, indapamide, potassium citrate or other drugs that induce lithogenesis or bone mineral loss.

We analyzed the following variables: age, BMI (body mass index, kg/m^2), creatinine serum (mg/dL), calcium serum (mg/dL), phosphorus serum (mg/dL), phosphatase alkaline serum (U/L), iPTH (intact parathyroid hormone, pg/mL), 25-OH vitamin D (U/L), pH serum, urine pH, 24-hour urine calcium, 24-hour citraturia, 24-hour oxaluria, 24-hour uricosuria, and calcium/creatinine ratio in urine during fasting. Urine and blood determinations were performed at least one month after the fracture.

Statistical analysis of the results was performed using Student's t test for qualitative-quantitative variables, and the Chi-square test for dichotomous variables. The normality of variables was done using the Kolmogorov-Smirnov test and the analysis of variance with the Levene's test. Statistical significance was set at $p \leq 0.05$. Analyses were performed with SPSS 17.0 for Windows (SAS Institute, Cary, NC).

Results

The mean age of patients was 70.1 ± 13.8 and 56.7 ± 6.4 years, in Group 1 and Group 2, respectively ($p = 0.0001$). BMI was 27.95 ± 3.88 kg/m^2 and 28.69 ± 4.52, in Group 1 and Group 2, respectively. Blood and urine showed higher values of serum alkaline phosphatase and fasting urine calcium/creatinine ratio in Group 1 compared to Group 2, with both comparisons statistically significant ($p < 0.05$). Moreover, patients in Group 2 showed statistically significant higher levels of oxalate, citrate, and urinary pH (Table 1).

We examined the percentage of patients with hypercalciuria (>260 mg/24-h), hyperoxaluria (>40 mg/24-h), hypocitraturia (<320 mg/24-h), and hyperuricosuria (>750 mg/24-h). The percentage of patients with hypercalciuria was significantly higher in Group 1 ($p = 0.04$) (Table 2). There were no statistically significant differences between groups regarding the presence of hyperoxaluria, hyperuricosuria, and hypocitraturia.

Discussion

Our results showed a higher percentage of women with hypercalciuria among those who have osteoporotic fracture without lithiasis compared to women without osteoporosis and without lithiasis. Moreover, the hypercalciuria observed was fasting hypercalciuria due to a fasting calcium/creatinine ratio above 0.11, eliminating any possible dietary contribution to elevated calcium levels. The classification and study of the metabolic parameters of blood and urine in patients with urolithiasis is vital to establishing the lithogenic risk.[9]

Table 1. Mean of serum and urinary variables measured in postmenopausal women with osteoporotic fracture (Group 1) versus postmenopausal women without osteoporosis (Group 2)

	Group 1	Group 2	*p* value
Serum creatinine (mg/dL)	0.98 ± 0.36	0.87 ± 0.31	n.s.
Serum calcium (mg/dL)	8.95 ± 0.73	9.19 ± 0.38	n.s.
Serum phosphorus(mg/dL)	3.43 ± 0.86	3.30 ± 0.39	n.s.
Serum alkaline phosphatase (U/L)	80.09 ± 32.31	60.25 ± 18.35	0.002
iPTH (pg/mL)	53.51 ± 28.27	45,49 ± 16.02	n.s.
25-OH vitamin D (U/L)	21.91 ± 14.01	23.14 ± 12.13	n.s.
Serum pH	7.37 ± 0.04	7.38 ± 0.03	n.s.
Calciuria 24-hour	140.85 ± 219.25	147.89 ± 73.45	n.s.
Uricosuria 24-hour	280.4 ± 178.7	234.87 ± 158.98	n.s.
Oxaluria 24-hour	22.37 ± 10.86	29.70 ± 12.37	0.01
Citraturia 24-hour	303.44 ± 274.71	1017.05 ± 897.46	0.0001
Urine pH	5.96 ± 0.88	6.43 ± 0.88	0.02
Fasting calcium/creatinine	0.12 ± 0.05	0.08 ± 0.04	0.006

iPTH: intact parathyroid hormone; n.s.: not significant.

Table 2. Presence of hypercalciuria in patients of Group 1 and Group 2 (p = 0.04)

	Hypercalciuria	Normocalciuria
Group 1	40% (22)	60% (33)
Group 2	18.8% (6)	81.2% (26)

The presence of hypercalciuria is an important factor to consider; it was present in up to 40% of patients in Group 1. The importance of measuring urinary calcium and fasting calcium/creatinine ratio has been previously demonstrated by their association with bone mineral density loss in patients with calcium renal stones,[10] and it may also have important implications for medical treatment.[11] However, the measurement of urinary calcium in patients with osteoporosis and without lithiasis is not widespread despite reports showing that hypercalciuria is present in postmenopausal women with osteoporosis.[12] Measuring urinary calcium in women with osteoporotic fracture is important, because it allows us to tailor our treatment.

A complete metabolic study, including blood and urine determinations, is necessary to evaluate lithogenic risk factors.[9] It is well known that patients with hypercalciuria and fasting hypercalciuria have more risk of bone mineral density loss,[13] and that calcium renal stones and osteopenia/osteoporosis are two related and reciprocal diseases.[14] The role of urinary calcium in the physiology of stones is very important, due to the main metabolic risk factor found in patients with lithiasis.[9] The study of calciuria is recommended in women with osteoporosis and osteoporotic fracture. Other metabolic risk factors, such as oxaluria, citraturia and uricosuria, should be measured; however, their prevalence in these patients could be less important even though lithogenic risk factors occur with calciuria. Routinely, the treatment of osteoporosis includes calcium and vitamin D supplements,[15] which may decrease the risk of fracture[16] without increasing urine calcium and the risk of nephrolithiasis.[17,18] However, other studies have claimed that it is impossible to determine whether the administration of calcium and vitamin D may increase urinary calcium and the risk of nephrolithiasis.[19,20] It seems clear that if hypercalciuria is present, calcium and vitamin D supplements may be substituted with a thiazide, which has shown to increase renal tubular reabsorption of calcium, increase serum calcium levels, decrease lithogenic risk and improve bone mineral density.[11,15] In this way, osteoporosis is treated without increasing the lithogenic risk.

We believe that knowing the urinary calcium level is essential to individualize treatment and to reduce the potential lithogenic risk. This study has its limitations, such as the number of patients, its cross-sectional nature and its single-centre, but these results introduce a new investigation path – the relationship between osteoporotic fracture and lithogenic risk factors in prospective studies and follow-up.

Conclusion

The measurement of 24-hour urinary calcium and fasting calcium/creatinine ratio are easy studies that should be included in the routine evaluation of postmenopausal women with osteoporotic fracture.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Arrabal Polo MA, Arrabal Martin M, de Haro Mu-oz T, et al. Mineral density and bone remodelling markers in patients with calcium lithiasis. *BJU Int* 2011;108:1903-8. http://dx.doi.org/10.1111/j.1464-410X.2011.10167.x
2. Arrabal Polo MA, Arrabal Martín M, Giron Prieto MS, et al. Osteopenia/osteoporosis in patients with calcium nephrolithiasis. *Urol Res* 2012;40:709-16. http://dx.doi.org/10.1007/s00240-012-0497-8
3. Letavernier E, Traxer O, Daudon M, et al. Determinants of osteopenia in male renal-stone-disease patients with idiopathic hypercalciuria. *Clin J Am Soc Nephrol* 2011;6:1149-54. http://dx.doi.org/10.2215/CJN.10191110
4. Zhao A, Dai M, Chen YJ, et al. Risk factors associated with nephrolithiasis: A case-control study in China. *Asia Pac J Public Health* 2015;27:NP414-NP424. http://dx.doi.org/10.1177/1010539512445189. Epub 16 May 2012.
5. Chou PSA, Kuo CN, Hung KS, et al. Osteoporosis and the risk of symptomatic nephrolithiasis: A population-based 5-year follow up study in taiwan. *Calcif Tissue Int* 2014;95:317-22. http://dx.doi.org/10.1007/s00223-014-9895-y
6. Arrabal Polo MA, Del Carmen Cano Garcia M, Canales BK, et al. Calcium nephrolithiasis and bone demineralization: Pathophysiology, diagnosis, and medical management. *Curr Opin Urol* 2014;24:633-8. http://dx.doi.org/10.1097/MOU.0000000000000111
7. Arrabal Polo MA, Arrabal Martin M, Arias Santiago S. Bone and metabolic markers in women with recurrent calcium stones. *Korean J Urol* 2013;54:177-82. http://dx.doi.org/10.4111/kju.2013.54.3.177
8. Ryan LE, Ing SW. Idiopathic hypercalciuria and bone health. *Curr Osteoporos Rep* 2012;10:286-95. http://dx.doi.org/10.1007/s11914-012-0120-5
9. Arrabal Martin M, Fernandez Rodriguez A, Arrabal Polo MA, et al. Estudio de factores fisico-quimicos en pacientes con litiasis renal. *Arch Esp Urol* 2006;59:583-94. http://dx.doi.org/10.4321/S0004-06142006000600004
10. Arrabal Polo MA, Arrabal Martin M, Poyatos Andujar A et al. Is the fasting calcium/creatinine a bone resorption marker in patients with calcium renal stones? *Urol Res* 2012;40:243-5. http://dx.doi.org/10.1007/s00240-011-0441-3
11. Sakhaee K, Maalouf NM, Kumar R, et al. Nephrolithiasis-associated bone disease: Pathogenesis and treatment options. *Kidney Int* 2011;79:393-403. http://dx.doi.org/10.1038/ki.2010.473
12. Carvalho M, Moreira Kulak CA, Cochenski Boba VZ. Prevalence of hypercalciuria in postmenopausal women with osteoporosis. *Arq Bras Endocrinol Metab* 2012;56:1-5.
13. Letavernier E, Traxer O, Daudon M, et al. Determinants of osteopenia in male renal-stone-disease patients with idiopathic hypercalciuria. *Clin J Am Soc Nephrol* 2011;6:1149-54. http://dx.doi.org/10.2215/CJN.10191110
14. Bijelic R, Milicevic S, Balaban J. Incidence of osteoporosis in patients with urolithiasis. *Med Arch* 2014;68:335-8. http://dx.doi.org/10.5455/medarh.2014.68.335-338
15. O'Neill S, MacLennan A, Bass S, et al. Guidelines for the management of postmenopausal osteoporosis for GPs. *Aust Fam Physician* 2004;33:910-9.
16. Spangler M, Phillips BB, Ross MB, et al. Calcium supplementation in postmenopausal women to reduce the risk of osteoporotic fractures. *Am J Health Syst Pharm* 2011;68:309-18. http://dx.doi.org/10.2146/ajhp070175
17. Haghighi A, Samimagham H, Gohardehi G. Calcium and vitamin D supplementation and risk of kidney stone formation in postmenopausal women. *Iran J Kidney Dis* 2013;7:210-3.
18. Penniston JL, Jones AN, Nakada SY, et al. Vitamin D repletion does not alter urinary calcium excretion in healthy postmenopausal women. *BJU Int* 2009;104:1512-6. http://dx.doi.org/10.1111/j.1464-410X.2009.08559.x

19. Sorensen MD, Eisner BH, Stone KL, et al. Impact of calcium intake and intestinal calcium absorption on kidney stones in older women: The study of osteoporotic fractures. *J Urol* 2012;187:1287-92. http://dx.doi.org/10.1016/j.juro.2011.11.109
20. Reza Ganji M. Postmenopausal osteoporosis treatment risk of urinary calculus development. *Iran J Kidney Dis* 2013;7:171-4.

Correspondence: Dr. Miguel Angel Arrabal-Polo, Dr Virgili Street. Huercal Overa, 04600, Spain; arrabalp@ono.com