Urol Res (2008) 36:233–239
DOI 10.1007/s00240-008-0146-4

ORIGINAL PAPER

Intestinal hyperabsorption of calcium and low bone turnover in hypercalciuric postmenopausal osteoporosis

Clarita V. Odvina · John R. Poindexter · Roy D. Peterson · Joseph E. Zerwekh · Charles Y. C. Pak

Received: 10 January 2008 / Accepted: 27 June 2008 / Published online: 17 July 2008

Abstract Hypercalciuria of intestinal origin has been linked with bone loss in calcium nephrolithiasis and idiopathic osteoporosis. This retrospective data analysis was performed to explore potential pathogenetic link between intestinal hyperabsorption of calcium and postmenopausal osteoporosis. Data were retrieved from postmenopausal women who were evaluated for osteoporosis or osteopenia at the Mineral Metabolism Clinic of UT Southwestern Medical Center. A total of 319 patients underwent the test of calciuric response to oral calcium load to obtain an indirect measure of intestinal calcium absorption. Serum and urinary biochemistry and L2–L4 bone mineral density (BMD) were compared between five quintiles of calciuric response. There was a statistically significant trend toward a rise in 24-h urinary calcium and a decrease in urinary deoxypyridinoline (DPD) and BMD, with increasing order of quintiles. The presentation of those in the 1st quintile was consistent with vitamin D insufficiency or deficiency, with impaired calcium absorption, secondary hyperparathyroidism, and stimulated bone turnover (high normal urinary DPD). In contrast, patients in the 5th quintile displayed a picture of absorptive hypercalciuria of stone disease, with intestinal hyperabsorption of calcium, high or high normal urinary calcium and suppressed bone turnover (low or low normal urinary DPD). Thus, the assessment of intestinal calcium absorption in a seemingly homogeneous group of postmenopausal women with osteoporosis or osteopenia revealed a spectrum of calciuric response whose extremes may represent two physiologically distinct subtypes that have important diagnostic and therapeutic implications.

Keywords Intestinal calcium absorption · Hypercalciuria · Bone mineral density · Postmenopausal osteoporosis

C. V. Odvina (✉) · J. R. Poindexter · R. D. Peterson · J. E. Zerwekh · C. Y. C. Pak
Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8885, USA
e-mail: clarita.odvina@utsouthwestern.edu

Introduction

There is emerging evidence that hypercalciuria of intestinal origin may be associated with bone loss or osteoporosis. Among patients with absorptive hypercalciuria (AH) with intestinal hyperabsorption of calcium and kidney stones, low spinal bone mineral density (BMD) has been described [1–3]. In a recent study based on histomorphometric analysis of bone, the bone loss in AH was shown to be due to reduced bone formation rather than increased bone resorption [4], confirming prior reports of some [5–7] though not others [8, 9]. In idiopathic osteoporosis, we previously reported the existence in some patients of the same biochemical presentation of AH, with hypercalciuria, intestinal hyperabsorption of calcium and low bone turnover [10]. Low bone formation was also reported in premenopausal women with idiopathic osteoporosis [11].

The link between hypercalciuria, high intestinal calcium absorption and bone loss is less well-established in postmenopausal osteoporosis. Hypercalciuria, reported in 6.3–19% of women with osteoporosis [12–18], appears to play an important role in the development of bone loss. In a retrospective analysis of data from 241 otherwise healthy women with postmenopausal osteoporosis, Giannini et al. found hypercalciuria to be present in 19% of the patients. Hypercalciuria was the most important predictor of low bone mass, accounting for more than 50% of the variance

in spinal bone density [13]. Unfortunately, the cause for the hypercalciuria was not defined. In a cross-sectional study of 173 women with postmenopausal osteoporosis, Tannebaum et al. [14] showed that hypercalciuria was present in 9.8% of patients. Seven patients were diagnosed to have renal hypercalciuria, six idiopathic, and four unidentified hypercalciuria. Some of their patients may have had impaired intestinal calcium absorption, since 8.1% had malabsorption, 4.1% vitamin D deficiency, and 6.9% high serum PTH. To the best of our knowledge, no prior report has systematically investigated intestinal calcium absorption and correlated it with bone turnover and calcium metabolism among patients with postmenopausal osteoporosis.

In our ambulatory protocol for osteoporosis, we utilized the calciuric response to oral calcium load as an optional surrogate test to estimate intestinal calcium absorption [19–21]. We also obtained spinal BMD and 24-h urine collection for calcium and deoxypyridinoline (DPD). This retrospective analysis of data from 319 patients so evaluated was conducted to explore the relationship of intestinal calcium absorption to postmenopausal osteoporosis or osteopenia.

Subjects and methods

Patient data

Data were retrieved from 319 patients who were evaluated for osteoporosis in an outpatient setting by the Center of Mineral Metabolism and Clinical Research at the University of Texas Southwestern Medical Center. Patients included in this report satisfied the following criteria: (a) postmenopausal women with osteoporosis or osteopenia, whereby osteoporosis is defined by atraumatic fractures or BMD criteria (T-score of ≤ -2.5, at L2–L4 vertebrae or femoral neck), and osteopenia is defined by T-score of ≤ -1.0 to -2.5 at L2–L4 vertebrae or femoral neck, (b) absence of secondary causes of osteoporosis or bone loss, such as primary hyperparathyroidism, intestinal fat malabsorption, distal renal tubular acidosis, impaired renal function (endogenous creatinine clearance <0.7 ml/min/kg body weight), systemic malignancy, or liver disease (cirrhosis or hepatitis), (c) no prior treatment with bisphosphonate, teriparatide, fluoride, or long-term glucocorticoid therapy, (d) adequate 24-h urine collection (for urinary calcium and other tests), indicated by urinary creatinine within 30% of idealized urinary creatinine in women of 17.2 mg/kg body weight [22], and (e) availability of results of "fast and load test" (fasting urinary calcium and 4-h urinary calcium following oral load of 1 g calcium) [19–21]. When its cost could not be covered by insurance carriers, the fast and load test became optional, ordered by only some attending physicians. The study population for this retrospective analysis comprised only those who completed this test.

Study design

All patients underwent the following evaluation. A careful history was taken for calcium intake. One week before the evaluation, patients were asked to discontinue calcium supplement, if any, but were allowed to continue their prevailing diet. A 24-h urine sample was then collected for the measurement of calcium, creatinine, and sodium. Patients underwent the fast and calcium load test (calciuric response) [19–21]. This involves collection of a 2-h fasting urine sample after an overnight fast, and a 4-h urine sample after an oral ingestion of 1 g calcium mixed in a synthetic meal. Both samples were analyzed for calcium and creatinine. A fasting venous blood sample was obtained for calcium, phosphorus, alkaline phosphatase (ALP), PTH, and creatinine. L2–L4 BMD was obtained. When the test for DPD became available, DPD was measured in 24-h urine. 25-Hydroxyvitamin D (25-OHD) was obtained in fresh serum samples when ordered by physicians; otherwise it was measured in frozen sera.

Analytical methods

Serum calcium, phosphorus, ALP and creatinine, and urinary creatinine, were determined in an autoanalyzer (SYNCHRON CX9 ALX system, Beckman Coulter, Inc., Fullerton, CA, USA). Urine calcium was analyzed by atomic absorption spectrophotometry (Instrumentation Laboratories, Lexington, MA, USA).

Serum PTH was measured by immunoradiometric assay for the whole molecule using ELISA, (Alpco Diagnostics, Windham, NH, USA) and 25-OHD by ELISA (Alpco Diagnostics, Windham, NH, USA). A value of $\leq$20 ng/ml is considered vitamin D deficient, while values between 21 and 29 ng/ml indicate relative insufficiency of vitamin D [22]. Urinary DPD was analyzed by EIA using a commercially available assay (Pyrilinks-D, Quidel Corporation, Santa Clara, CA, USA). The intra-assay variation for DPD is 4.8% and the inter-assay variation is 8.4%. Endogenous creatinine clearance was calculated from 24-h urinary creatinine and corresponding serum creatinine. L2–L4 vertebral BMD were obtained by quantitative digital radiography (Hologic, Waltham, MA, USA). For this study, Z-scores (against age-matched value) and T-scores (against normal peak value) are reported.

Calciuric response, an indirect measure of intestinal calcium absorption, was calculated from the difference between urinary calcium post-calcium load and fasting urinary calcium expressed in milligram per deciliter glomerular filtrate (GF). This method had been shown to strongly correlate

with the isotopic method of evaluating calcium absorption [20, 23]. In the original description, urinary calcium during post-load and fasting was expressed as milligram per milligram creatinine [19]. Broadus et al. [20] introduced a refined method, where the increment in urinary calcium, expressed as milligram per deciliter GF, was calculated from the fasting value to the latter 2 h after oral calcium load. In this study, we employed a simplified version [21], where calciuric response was calculated from the difference between 4-h urinary calcium post-calcium load and 2-h fasting calcium, each expressed as milligram per deciliter GF. In our laboratory, the mean normal value for calciuric response is 0.069 mg/dl GF (range −0.033 to 0.171).

Statistical analysis

One-way analysis of variance was conducted to compare the Ca load-fast quintiles and tests of linear trends were made with polynomial contrasts. Analysis of covariance models were used to further assess these trends while adjusting for age and BMI. Two-sided *P*-values less than 0.05 were considered statistically significant. Results are presented as mean ± SD. Statistical analysis was performed with SAS 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Division into 5 quintiles of calciuric response

Data from 319 patients with postmenopausal osteoporosis or osteopenia, with a mean age of 63 ± 10.6 years, were included in the analysis. Using the SAS software, patients were divided into five equal groups (quintiles) based on their calciuric response to oral calcium load (Fig. 1). Patients in the first quintile had a low or low normal calciuric response, indicating that they had impaired calcium absorption. Patients in the second and third quintiles displayed calciuric response that was slightly below the normal mean value or slightly above (indicated by dashed horizontal line in Fig. 1). Thus, they had normal intestinal calcium absorption. Those in the fourth quintile had a high normal calciuric response while most of the patients in the fifth quintile had a high calciuric response (exceeding upper normal limit, shown by upper dotted horizontal line in Fig. 1). Thus, patients in the upper two quintiles had high or high normal intestinal calcium absorption.

Demography and serum biochemistry

Table 1 summarizes the demographic and laboratory data of each quintile. The estimated calcium intake was similar among the five quintiles of calciuric response, being about 600 mg/day. There was a statistically significant trend toward a decrease in age and BMI, with increasing order of quintiles. Thus, patients in the first quintile were older and had higher BMI compared to the patients in the other quintiles.

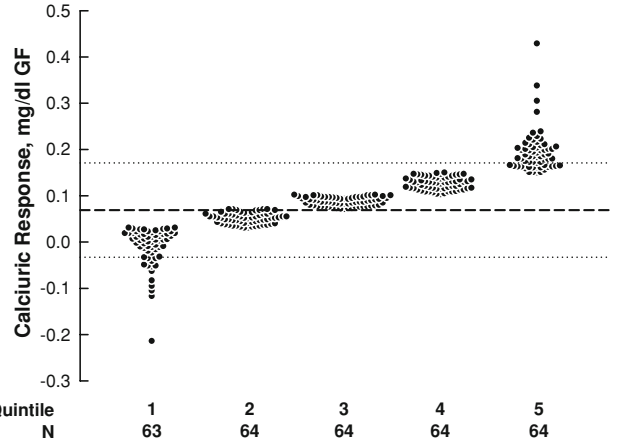

Fig. 1 Individual data for calciuric response for each quintile of calciuric response. *Dashed horizontal line* indicates mean normal value, and *dotted horizontal lines* represent normal limits

Mean serum calcium and phosphorous concentrations were normal and did not differ between the five quintiles of calciuric response (Table 1). There was a statistically significant trend toward a decrease in serum PTH and ALP, and an increase in serum 25-OHD and creatinine clearance, with increasing order of quintiles. Thus, the first quintile had high serum PTH (upper normal limit = 65 ng/ml), high normal ALP and lower creatinine clearance. In the fourth and fifth quintiles, serum PTH and ALP were normal. Creatinine clearance was higher in the third, fourth, and fifth quintiles. Serum 25-OHD was in the vitamin D insufficient range in all quintiles, but the value in the first quintile was closer to the vitamin D deficient range.

Urinary biochemistry and L2–L4 BMD

Twenty-four-hour urinary calcium (expressed as milligram per day or milligram per kilogram body weight) showed a significant trend toward a rise, with increasing order of quintiles (Table 2; Fig. 2). Thus, the first quintile had low urinary calcium, while the fifth quintile of calciuric response had high normal urinary calcium (close to the upper normal limit of 220 mg/day on a calcium intake of 600 mg/day [24]). Mean urinary sodium (meq/day) was normal and did not differ between the five quintiles of calciuric response (Table 2). There was a statistically significant trend toward an increase in the post load urinary calcium in milligram per deciliter GF with increasing order of quintiles, while fasting urinary calcium displayed no particular trend.

Table 1 Demography and serum chemistry

	Quintile of calciuric response										
	1		2		3		4		5		*P*
Load—fast, mg/dl GF	63	−0.01 ± 0.04	64	0.05 ± 0.01	64	0.09 ± 0.01	64	0.13 ± 0.01	64	0.19 ± 0.05	<0.0001
Age, years	63	69.3 ± 10.7	64	64.4 ± 11.1	64	63.0 ± 9.4	64	59.9 ± 9.1	64	58.7 ± 9.3	<0.0001
Weight, kg	62	63.3 ± 17.0	64	61.9 ± 16.0	64	61.9 ± 11.2	64	59.5 ± 9.8	64	59.6 ± 10.2	0.06
BMI, kg/m^2	62	25.9 ± 6.2	64	24.3 ± 5.9	64	23.9 ± 3.8	64	23.2 ± 3.9	64	23.1 ± 3.8	0.0005
Estimated Ca intake, mg/day	59	634 ± 264	59	653 ± 283	63	583 ± 250	60	642 ± 257	61	667 ± 303	0.61
Serum											
Ca, mg/dl	63	9.3 ± 0.6	64	9.3 ± 0.4	64	9.4 ± 0.4	64	9.2 ± 0.4	64	9.3 ± 0.4	0.69
P, mg/dl	62	3.4 ± 0.6	63	3.4 ± 0.5	63	3.5 ± 0.6	63	3.5 ± 0.5	63	3.5 ± 0.6	0.53
ALP, IU/L	63	94 ± 52	63	80 ± 32	63	70 ± 27	63	70 ± 32	62	75 ± 47	0.003
PTH, ng/ml	63	66 ± 99	63	50 ± 30	63	42 ± 17	63	42 ± 16	61	43 ± 21	0.005
25-OHD, pg/ml	50	20 ± 10	52	23 ± 10	57	24 ± 11	57	24 ± 10	47	25 ± 9	0.019
Creatinine clearance, ml/min	63	77 ± 28	64	79 ± 24	64	86 ± 27	64	90 ± 22	64	82 ± 19	0.021

Data are presented as *n*, mean, and SD. The *P* values represent the statistical significance of the trend between quintiles

To convert values for serum calcium to millimole per liter, multiply by 0.2. Multiply by 0.323 to convert values for phosphorous to millimole per liter. To convert values for PTH to picomoles per liter, multiply by 0.102 and by 2.496 to convert 25-hydroxyvitamin D to nanomoles per liter

BMI body mass index, *Ca* calcium, *P* phosphorous, *ALP* alkaline phosphatase, *PTH* parathyroid hormone, *25-OHD* 25-hydroxyvitamin D

Table 2 Urinary and bone mineral density data

	Quintile of calciuric response										
	1		2		3		4		5		*P*
Urinary											
Ca, mg/day	63	116 ± 85	64	118 ± 82	64	147 ± 74	64	162 ± 62	64	182 ± 80	<0.0001
Ca, mg/kg BW	62	1.85 ± 1.48	64	1.99 ± 1.51	64	2.40 ± 1.23	64	2.77 ± 1.09	64	3.05 ± 1.25	<0.0001
Na, meq/day	63	117 ± 71	64	116 ± 50	64	119 ± 53	64	123 ± 52	64	117 ± 49	0.74
Cr, g/day	63	0.82 ± 0.26	64	0.86 ± 0.26	64	0.90 ± 0.20	64	0.93 ± 0.19	64	0.95 ± 0.17	<0.0001
Fasting Ca, mg/dl GF	63	0.10 ± 0.09	64	0.07 ± 0.06	64	0.07 ± 0.05	64	0.06 ± 0.04	64	0.08 ± 0.05	0.03
Post load Ca, mg/dl GF	63	0.09 ± 0.06	64	0.12 ± 0.06	64	0.16 ± 0.05	64	0.19 ± 0.04	64	0.28 ± 0.07	<0.0001
DPD, nmol/mmol Cr	16	6.8 ± 3.8	19	4.9 ± 2.0	18	4.6 ± 1.7	20	4.2 ± 2.0	21	3.3 ± 2.2	<0.0001
L2–L4 *Z* score	63	−0.1 ± 1.7	64	−0.3 ± 1.6	64	−0.6 ± 1.4	64	−1.0 ± 1.3	64	−1.1 ± 1.3	<0.0001
L2–L4 *T* score	63	−2.1 ± 1.7	64	−2.0 ± 1.7	64	−2.3 ± 1.3	64	−2.4 ± 1.3	64	−2.4 ± 1.3	0.08

Data are presented as *n*, mean, and SD. The *P* values represent the statistical significance of the trend between quintiles

To convert values for 24-h urinary calcium to millimoles per day, multiply 0.025. To convert 24-h urinary sodium to millimoles per day, multiply by 1, and multiply by 8.8 to convert 24 h urinary creatinine to millimoles per day

There was a highly significant trend toward a decrease in urinary DPD, with increasing order of quintiles (Table 2, Fig. 3). Thus, urinary DPD approximated the upper normal limit in the first quintile (normal mean 5.0, range 3.0–7.4 nmol/mol creatinine) and was close to the low normal limit in the fourth and fifth quintiles.

There was a statistically significant trend toward a decrease in L2–L4 BMD Z-scores (comparison of patient's BMD to what is expected for the patient's age, sex, and ethnicity) with increasing order of quintiles of calciuric response (Table 2; Fig. 4). Thus, the age-matched L2–L4 BMD was more markedly depressed in the fourth and fifth quintiles than in the first quintile. The patients in the first quintile were older than those in the fourth and fifth quintiles. Hence, no significant trend in spinal BMD T-scores (comparison of a patient's BMD to the mean for young adults of the same sex and ethnicity) was observed.

Except for the creatinine clearance ($P = 0.57$), the linear trend remained significant for the all the variables when the data was analyzed adjusting for age and BMI.

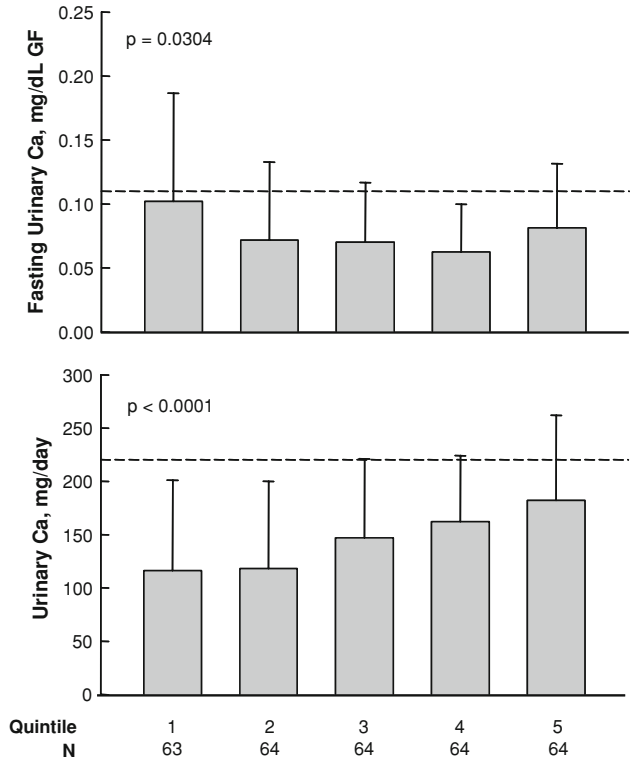

Fig. 2 Fasting and 24-h urinary calcium for each quintile of calciuric response. Mean + SD is shown for each quintile. The *P*-value represents the test for linear trend across the five groups from the analysis of variance models. Upper normal limits are given by *dashed horizontal lines*

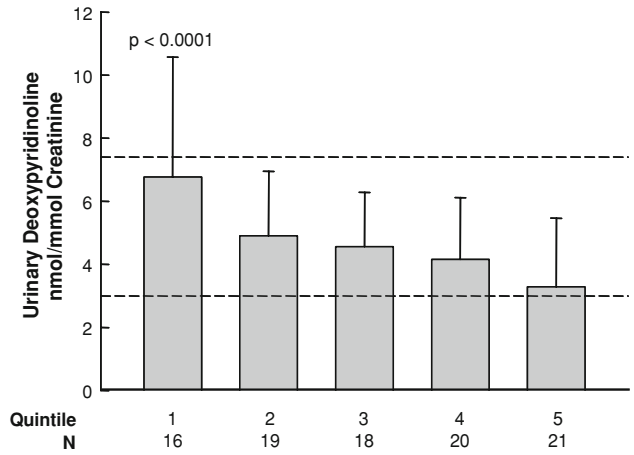

Fig. 3 Urinary deoxypyridinoline for each quintile of calciuric response. Mean + SD is shown for each quintile. *Horizontal dashed lines* indicate the normal range. Statistical significance of the trend between quintiles is given by *P*-value

Discussion

This retrospective data analysis was conducted in order to ascertain the potential pathogenetic role of intestinal calcium absorption in postmenopausal osteoporosis. In 319 patients with postmenopausal osteoporosis or osteopenia, the calciuric response to oral calcium load was obtained as an indirect measure of intestinal calcium absorption. Their serum and urinary biochemistry and BMD were compared between the five quintiles of calciuric response as a continuous variable. The opposite extremes of calciuric response appeared to be physiologically distinct, with one displaying secondary hyperparathyroidism of vitamin D insufficiency or deficiency and the other, the biochemical features of AH ("AH phenotype").

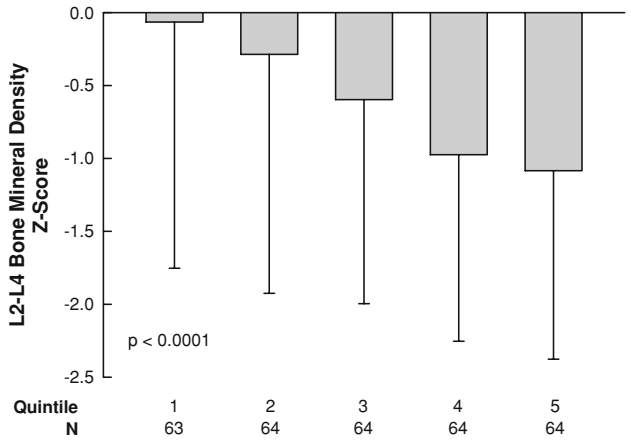

Fig. 4 Z-score for L2–L4 BMD for each quintile of calciuric response. Mean − SD is shown

Patients with postmenopausal osteoporosis or osteopenia in the first quintile of calciuric response revealed a picture of secondary hyperparathyroidism and probable high bone turnover associated with impaired intestinal calcium absorption. Besides low calciuric response, they had serum 25-OHD in the vitamin D insufficient-deficient range, high serum PTH and high normal ALP, consistent with vitamin D insufficiency or deficiency [22]. These patients had high normal or high urinary DPD, suggestive of PTH-dependent stimulation of bone turnover. The incidence of vitamin D deficiency in patients attending an osteoporosis program has been reported to be between 4.1 and 52% [14, 25, 26].

In contrast to the aforementioned presentation, most patients in the fifth quintile had exaggerated calciuric response to oral calcium load, indicative of intestinal hyperabsorption of calcium. On a dietary calcium intake of about 600 mg/day, the majority of patients had high normal urinary calcium and a minority had hypercalciuria (>220 mg/day [24]). Most of them therefore had a biochemical picture of AH type II, a less severe form of the entity where hypercalciuria is revealed on high but not on a restricted calcium intake [27]. Patients in the fourth quintile had high normal calciuric response and high normal urinary calcium. Thus, about 20% of patient with postmenopausal osteoporosis or

osteopenia had the AH phenotype, and another 20% of patients had a tendency toward it.

The exact cause for intestinal hyperabsorption of calcium is not known. In some patients with AH of stone disease, vitamin D excess or sensitivity had been implicated [27–32]. The finding of serum 25-OHD in the vitamin D insufficient range among patients in the fourth and fifth quintiles makes this possibility unlikely. A potential involvement of genetic factors has been explored. Reed et al. found polymorphisms and mutations in the soluble adenylyl cyclase gene in some stone-forming patients with AH [33]. However, we have not yet explored this genotype in our patients with postmenopausal osteoporosis.

It has been proposed that calcitriol overproduction or increased sensitivity to its effect could potentially contribute to bone loss in patients with AH. Unfortunately, calcitriol levels were not measured in this retrospective study.

Despite uncertainty regarding the underlying causes, it is becoming increasingly apparent that intestinal hyperabsorption may sometimes be linked with low bone formation. As already discussed, a histomorphometric analysis of bone has disclosed impaired bone formation among stone-forming patients with AH [4, 7], as well as in hypercalciuric men with idiopathic osteoporosis [10]. This report in patients with postmenopausal osteoporosis or osteopenia further supports the above scheme, since patients presenting with increased calcium absorption had depressed urinary DPD.

Based on foregoing discussion, the "AH syndrome" may in fact be part of a more generalized syndrome affecting bone and bowel. In AH presenting with stone disease, the bowel may be primarily affected, with hypercalciuria from intestinal hyperabsorption of calcium leading to stone formation. Even in these patients, bone tissue is not spared, since many patients may have low spinal BMD or osteoporosis [1, 4]. In patients with idiopathic or postmenopausal osteoporosis, the bone tissue may be the primary target causing osteoporosis. However, the bowel is also involved, since intestinal calcium absorption is elevated.

This study implying different physiological basis for postmenopausal osteoporosis has certain therapeutic implications. The patients in the first quintile with secondary hyperparathyroidism and probable high bone turnover might benefit from vitamin D supplementation. On the other hand, if the subgroup of patients with AH were proven to suffer from low bone turnover, such patients may be more susceptible to the development of severely suppressed bone turnover from long-term bisphosphonate therapy [34]. The identification of these physiologically distinct subtypes might also have important diagnostic value. However, this discrimination requires the use of calciuric response, and not the 24-h urinary calcium. Unfortunately, this test is and more laborious than the measurement of urinary calcium.

The present study has certain limitations. First, as a retrospective data analysis, some tests were not planned or available. Second, the state of bone turnover was estimated from urinary DPD alone, and not by markers of bone formation or bone histomorphometry. Moreover, it was available in only 30% of patients, as this test was introduced many years after the first enrollment of patients. However, there is little reason to suspect that the distribution of DPD would have been different had they been available in all patients.

In summary, the categorization of patients with postmenopausal osteoporosis or osteopenia into quintiles of calciuric response disclosed two physiologically distinct ends of a continuous spectrum. The presentation of the first quintile was consistent with impaired calcium absorption due to vitamin D insufficiency or deficiency, stimulating parathyroid function and bone resorption. The patients in the fifth quintile presented a picture of AH of stone disease, with intestinal hyperabsorption of calcium, high or high normal urinary calcium and probable low bone turnover. Further studies are warranted in order to fully appreciate therapeutic and diagnostic implications of these findings.

Acknowledgments The authors would like to thank Faye Britton for advice and editorial assistance, and Orson Moe for his critical reading of the manuscript.

References

1. Pietschmann F, Breslau NA, Pak CYC (1992) Reduced vertebral bone density in hypercalciuric nephrolithiasis. J Bone Miner Res 7:1383–1388
2. Caudarella R, Vescini F, Buffa A, Sinicropi G, Rizzoli E, La Manna G et al (2003) Bone mass loss in calcium stone disease: focus on hypercalciuria and metabolic factors. J Nephrol 16:260–266
3. Giannini S, Nobile M, Sartori L, Calò L, Tasca A, Dalle Carbonare L et al (1998) Bone density and skeletal metabolism are altered in idiopathic hypercalciuria. Clin Nephrol 50:94–100
4. Heller HJ, Zerwekh JE, Gottschalk FA, Pak CYC (2007) Increased bone resorption and reduced bone formation in moderate-severe absorptive hypercalciuria: bone histomorphometric analysis and alendronate challenge. Kidney Int 71:808–815. doi:10.1038/sj.ki.5002181
5. Heilberg IP, Martini LA, Szejnfeld VL, Carvalho AB, Draibe SA, Ajzen H et al (1994) Bone disease in calcium stone forming patients. Clin Nephrol 42:175–182
6. Heiberg IP, Weisinger JR (2006) Bone disease in idiopathic hypercalciuria. Curr Opin Nephrol Hypertens 15:393–402
7. Malluce HH, Tschoepe W, Ritz E, Meyer-Sabellek W, Massry SG (1980) Abnormal histology in idiopathic hypercalciuria. J Clin Endocrinol Metab 50:654–658
8. Steiniche T, Moskilde L, Christensen MS, Melsen F (1988) A histomorphometric determination of iliac bone remodeling in patients with recurrent renal stone formation and idiopathic hypercalciuria. APMIS 97:309–316

9. Weisinger JR, Alonzo E, Bellorin-Font F, Blasini AM, Rodriguez MA, Paz-Marinez V et al (1996) Possible role of cytokines on the bone mineral loss in idiopathic hypercalciuria. Kidney Int 49:244–250. doi:10.1038/ki.1996.34
10. Zerwekh JE, Sakhee K, Breslau NA, Gottschalk F, Pak CYC (1992) Impaired bone formation in male idiopathic osteoporosis: further reduction in the presence of concomitant hypercalciuria. Osteoporos Int 2:128–134. doi:10.1007/BF01623819
11. Donovan MA, Dempster D, Zhou H, McMahon DJ, Fleischer J, Shane E (2005) Low bone formation in premenopausal women with idiopathic osteoporosis. J Clin Endocrinol Metab 90:3331–3336. doi:10.1210/jc.2004-2042
12. Barzel US (2003) Recommended testing in patients with low bone density. J Clin Endocrinol Metab 88:1404–1405. doi:10.1210/jc.2002-021660
13. Giannini S, Nobile M, Dalle Carbonare L, Lodetti MG, Sella S, Vittadello G et al (2003) Hypercalciuria is a common and important finding in postmeopausal women with osteoporosis. Eur J Endocrinol 149:209–213. doi:10.1530/eje.0.1490209
14. Tannebaum C, Clark J, Schwartzman K, Wallenstein S, Lapinski R, Meier D et al (2002) Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J Clin Endocrinol Metab 87:4431–4437. doi:10.1210/jc.2002-020275
15. Feitag A, Barzel US (2002) Differential diagnosis of osteoporosis. Gerontology 48:90–102
16. Deutschmann HA, Weger M, Weger W, Kotanko P (2002) Search for occult secondary osteoporosis: impact of identified possible risk factors on bone mineral density. J Intern Med 252:389–397. doi:10.1046/j.1365-2796.2002.01040.x
17. Painter SE, Kleerekoper M, Camacho PM (2006) Secondary osteoporosis: a review of the recent evidence. Endocr Pract 12:436–445
18. Favus MJ (2005) Postmenopausal osteoporosis and the detection of so-called secondary causes of low bone density. J Clin Endocrinol Metab 90:3800–3801. doi:10.1210/jc.2005-0784
19. Pak CYC, Kaplan R, Bone H, Townsend J, Waters O (1975) A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med 292:497–500
20. Broadus AE, Dominguez D, Bartter FC (1978) Pathophysiological studies in idiopathic hypercalciuria: use of an oral calcium tolerance test to characterize distinctive hypercalciuric subgroups. J Clin Endocrinol Metab 47:751–760
21. Harvey JA, Zobitz MM, Pak CYC (1988) Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. J Bone Miner Res 3:253–258
22. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
23. Schuetter SA, Knowles JB (1988) Intestinal absorption of $Ca(H2PO4)_2$ and Ca citrate compared by two methods. Am J Clin Nutr 47:884–888
24. Pak CYC, Ohata M, Lawrence EC, Snyder W (1974) The hypercalciurias: causes, parathyroid functions and diagnostic criteria. J Clin Invest 54:387–400. doi:10.1172/JCI107774
25. Haden ST, Fuleihan GEH, Angell JE, Cotran NM, LeBoff MS (1999) Calcidiol and PTH levels in women attending an osteoporosis program. Calcif Tissue Int 64:275–279. doi:10.1007/s002239900618
26. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT et al (2005) Prevalence of vitamin D insufficiency among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 90:3215–3224. doi:10.1210/jc.2004-2364
27. Pak CYC, Britton F, Peterson R, Ward DL, Northcutt C, Breslau NA et al (1980) Ambulatory evaluation of nephrolithiasis: classification, clinical presentation and diagnostic criteria. Am J Med 69:19–30. doi:10.1016/0002-9343(80)90495-7
28. Kaplan RA, Haussler MR, Deftos LJ, Bone H, Pak CYC (1977) The role of 1α, 25-dihydroxyvitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J Clin Invest 59:756–760. doi:10.1172/JCI108696
29. Broadus AE, Erickson SB, Gertner JM, Cooper K, Dobbins JW (1984) An experimental human model of 1, 25-dihydroxy vitamin D-mediated hypercalciuria. J Clin Endocrinol Metab 58:161–169
30. Broadus AE, Insogna KL, Lang R, Ellison AF, Dreyer BE (1984) Evidence of disordered control of 1, 25-dihydroxyvitamin D production in absorptive hypercalciuria. N Engl J Med 311:73–80
31. Breslau NA, Preminger GM, Adams BV, Otey J, Pak CYC (1992) Use of ketoconazole to probe the pathogenetic importance of 1, 25-dihydroxyvitamin D in absorptive hypercalciuria. J Clin Endocrinol Metab 75:1446–1452. doi:10.1210/jc.75.6.1446
32. Karnauskas AJ, van Leeuwen JP, van den Bemd GJ, Kathpalia PP, DeLuca HF, Bushinsky DA et al (2005) Mechanism and function of high vitamin D receptor levels in genetic hypercalciuric stone-forming rats. J Bone Miner Res 20:447–454. doi:10.1359/JBMR.041120
33. Reed BY, Gitomer WL, Heller HJ, Hsu MC, Lempke M, Padalino P et al (2002) Identification and characterization of a gene with base substitutions associated with absorptive hypercalciuria phenotype and low spinal bone density. J Clin Endocrinol Metab 87:1476–1485. doi:10.1210/jc.87.4.1476
34. Odvina CV, Zerwekh ZE, Rao DS, Maalouf N, Gottschalk F, Pak CYC (2005) Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 90:1291–1301