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ORIGINAL PAPER

Bone mineral density measurement in patients with recurrent normocalciuric calcium stone disease

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Abstract To investigate bone mineral densitometry findings in patients with normocalciuric urinary system stone disease, we compared 150 patients with normocalciuric calcium stone disease (group 1) and 60 subjects of a control group (group 2). The patients were compared according to bone mineral content (BMC), bone area (BA), bone mineral density (BMD), *T*-score and *Z*-score values of femur neck, total femur and lumbar spine (L2–L4) by dual energy absorptiometry. We found that 76.6% of the patients in group 1 and 20.0% in group 2 had low BMD; 11.3% of patients in group 1 had osteoporosis and 65.4% had osteopenia. In the control group, there was no osteoporosis, but 20.0% of the subjects had osteopenia. In group 1, there was hyperoxaluria in 26.0% of patients, hypocitraturia in 15.3% of patients, hyperuricosuria in 6.0% of patients, both hypocitraturia and hyperoxaluria in 8.6% of patients in a 24-h urine analysis. Urine analysis was normal in 44.0% of patients. Our results showed a severe loss of bone mass in patients with urinary system normocalciuric calcium stone disease. Thus, the necessary precautions concerning bone mass protection should be taken and the patients should be informed about this issue.

Keywords Normocalciuria · Urolithiasis · Dual energy X-ray absorbsiometry

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Introduction

The prevalence of urinary system stone disease is between 1 and 5% [1]. In industrialized populations, the risk of the lifelong occurrence of urinary system stone disease is about 20% for men and 5–10% for women [2]. It is more prevalent between 30 and 60 years of age. The most common type of urinary system stones is calcium-containing stones, comprising 75–80% of all urinary system stones [3]. Of calcium-containing stones, 80–90% are primary (idiopathic) and 10–20% are secondary. Recurrence rates of untreated calcium-containing stones are 10, 35 and 50% at 1, 5 and 10 years, respectively [4].

It was determined that the rate of hypercalciuria was 60%, when metabolic analyses of patients with idiopathic urinary system calcium-containing stone disease were performed [5, 6]. In a study performed in our country by Akinci et al. [7], it was determined that there was idiopathic hypercalciuria in 44.1% of the patients with calcium-containing stones. Intestinal hyperabsorption of calcium due to various reasons or increased calcium mobilization from bones produce hypercalciuria due to increased renal calcium load. An increased level of 1.25 $(OH)_2$ vitamin D also causes increased renal calcium load due to increments in intestinal calcium absorption [8]. On the other hand,

increased parathyroid hormone (PTH) level due to primary hyperparathyroidism results in increased bone calcium resorption and renal calcium load which causes calcium-containing stone formation. Hypovitaminosis D, as a disease in adult people, manifests itself with hypocalcemia and secondary hyperparathyroidism with subsequent loss of trabecular bone, thinning of cortical bone and, eventually, a higher risk of fractures [9].

Calcium homeostasis of the body is maintained primarily via PTH, vitamin D and calcitonin [10]. PTH takes over the central role in rapid control of calcium homeostasis. It increases blood calcium level via regulation of calcium inflow into extracellular fluid through coordinative effects over intestines, kidneys and bones [11]. The principal effect of vitamin D on calcium metabolism is to increase intestinal absorption of calcium and phosphate, to increase reabsorption of bone mineral matrix and to maintain bone calcium deposition through an effect on intestinal calcium absorption [11]. In the case of intoxication, it causes hypercalcemia via increased bone calcium mobilization and increased intestinal calcium absorption. Calcitonin decreases the blood calcium level through inhibition of bone resorption. Beside these hormones, etiologic factors such as high protein diet, high sodium diet and metabolic acidosis also have important effects on blood calcium balance [12].

Osteoporosis is characterized by a reduction in bone density, which has been associated with skeletal fragility and an increased risk of fracture after minimal trauma [13]. It is an important health problem in both men and women. Osteoporosis gains importance due to other resultant health problems (symptomatic vertebral bone fractures, commonly of back pain, loss of height, kyphosis, emotional problems and impaired mobility) [13].

Reduction in bone mass increases as a result of physical inactivity, cigarette smoking, alcohol consumption, calcium-poor diet, vitamin-D deficiency, secondary hyperparathyroidism, metabolic acidosis, glucocorticoids and anticonvulsant drug usage. Genetic predisposition is also known to be an important risk factor for osteoporosis.

In 1976 Alhava et al. [14] first measured BMD in stone patients. In this study, it was found that BMD was low in measurements performed on the radius. Hypercalciuric and normocalciuric patients were evaluated together and stone analysis was not performed. In studies performed recently on patients with calcium-containing stones, BMD was found to be low. But most of these studies were performed in hypercalciuric patients [15–17]. Jaeger et al. [18] in 1994, found that BMD was low in both hypercalciuric and normocalciuric patients.

There is no study in the literature comparing patients only with normocalciuric urinary system calcium stone disease and healthy volunteers. In our study, we compared BMD values of normocalciuric patients with idiopathic recurrent urinary system calcium stone disease and those of a healthy control group.

Materials and methods

Hundred and fifty patients (75 men and 75 women) comprised group 1. Patients with a history of at least two attacks of urinary system stone disease in whom a metabolic investigation revealed normocalciuric idiopathic calcium stone disease were included in this group. The age range of the patients was between 18 and 50 years. Mean age was 38.1, 35.3 and 36.7 years for women, men and the total group, respectively. Sixty healthy volunteers (35 men and 25 women) with personal or family (only first-degree relatives) histories of no urinary system stone disease comprised group 2. Their ages ranged between 18 and 50 years. Mean age was 39.2, 33.5 and 36.4 years for women, men and the total group, respectively.

We evaluated the subjects in both groups for weight, height and body mass index (BMI).

Patients having diseases which could affect calcium metabolism or that cause BMD changes (hyperthyroidism, hyperparathyroidism, hypercorticolism, some metabolic diseases, renal diseases and malignant diseases, etc.), patients using some drugs (estrogens, progesterone, glicocorticoids, diuretics, anticonvulsants, vitamin D, antiacid drugs, heparin, prostaglandin preparations, etc.), menopausal women and patients with other urinary system diseases were excluded from the study. In group 2, patients with conditions which decrease BMD such as immobilization for > 2 months during the last 5 years, prolonged corticosteroid therapy (>3 months), tobacco and alcohol consumption, poor dietary calcium intake, vitamin D insufficiency and secondary hyperparathyroidism, metabolic acidosis and steroid and anticonvulsant drug usage were excluded from the study.

The stones were analysed by X-ray crystallography method in Tübitak Marmara Research Center (MRC) using a Shimadzu XRD-6000 device with a Cu X-ray tube. Patients in whom analysis revealed calcium stones were included in our study.

The metabolic study was performed while the patients were on their home diet. Serum creatinine,

calcium, potassium, uric acid, alkaline phosphatase and PTH levels were measured. All biochemical variables were determined using an Olympus Autoanalyser (Olympus Instruments, Tokyo, Japan) and PTH was measured in serum using a radioimmunassay kit (Beckman Coulter Synchron LX 20, USA). All the subjects had normal renal function with a plasma creatinine concentration lower than 1.20 mg/dl.

Urine was collected twice over 24 h for measurement of calcium, uric acid, oxalate, citrate and creatinine excretion. Urinary calcium, creatinine and uric acid levels were measured with the O-cresolphtalein complexane method, Jaffe method and enzymatic uricase/PAP method, respectively. Urinary citrate and oxalate levels were measured with an enzymatic method using a spectrophotometer. Hypercalciuria was defined as a urinary calcium excretion greater than 4.0 mg/kg per day or 300 mg/day in two consecutive 24-h urine collections while the subjects were on a free choice diet.

BMD (g/cm^2), bone area (BA) (cm^2), bone mineral content (BMC) (g), *T*-score and *Z*-score were measured for femur neck, total femur, and total lumbar vertebra (L2–L4) using dual-energy X-ray absorptiometry (DEXA) (QDR Elite W 4500, Hologic, Waltham, Massachusetts, USA) in both groups. Data were corrected for age, height and body mass index (weight/height, BMI). The *T*-score compares bone mineral density of the patients to that of young healthy subjects. This represents the optimum age for peak BMD and the *T*-score is the important measurement for the determination of BMD loss [19]. According to World Health Organization (WHO) classification criteria, a *T*-score below −2.5 was evaluated as osteoporosis and a *T*-score between −2.5 and −1.0 as osteopenia. All data were expressed as the mean ± standard deviation (SD).

The numeric data of two groups were compared by Student's *t* test. A Chi-Square test was used for comparison of categoric data of groups. Spearman's correlation tests were performed for comparison of bone density parameters and biochemical parameters. Values of $P < 0.05$ were considered to be statistically significant.

Results

Table 1 shows the baseline anthropometric characteristics of both groups, subdividing groups according to gender. As expected, the males showed higher weight, height and BMI than females, but there was no statistical difference for mean values of age, weight, height and BMI of the two groups (Table 1).

It was found that BMD was low in 115 (76.7%) patients of group 1, while it was low in 12 (20.0%) subjects of the control group. There was a statistically significant difference between the two groups ($P < 0.01$). It was determined that 13 (11.3%) patients had osteoporosis and 102 (65.4%) patients had osteopenia according to *T*-score in group 1. In the control group, 12 (20%) subjects had osteopenia, but there was no subject with osteoporosis. The rates of osteoporosis and osteopenia were significantly higher in group 1 than in the control group ($P < 0.05$, $P < 0.01$) (Tables 2,

Table 1 Anthropometric parameters of groups according to gender

	Patients		Controls		*P*
	Men	Women	Men	Women	
Age (years)	35.3 ± 11.2[a]	38.1 ± 10.5[b]	33.5 ± 5.7	39.2 ± 6.7	NS
Height (cm)	175 ± 7.5[a]	160 ± 6.3[b]	177 ± 5.7	164 ± 6.5	NS
Weight (kg)	76 ± 6.4[a]	58 ± 5.7[b]	76 ± 4.3	57 ± 6.3	NS
BMI	24.8 ± 1.9[a]	22.6 ± 1.5[b]	24.2 ± 1	21.2 ± 1.7	NS

Means ± SD are shown

NS not significant

[a] Not significant when compared with healthy (control) men

[b] Not significant when compared with healthy (control) women

Table 2 BMD values of groups according to gender

	Patients		Controls	
	Men	Women	Men	Women
Femur neck BMD (gr/cm²)	0.7690 ± 0.133[a]	0.7497 ± 0.141[b]	0.8902 ± 0.165	0.8840 ± 0.118
Total femur BMD (gr/cm²)	0.9040 ± 0.109[a]	0.8904 ± 0.164[b]	0.9617 ± 0.156	0.9295 ± 0.150
Lumbal spine BMD (L2–L4) (gr/cm^2)	0.8530 ± 0.155[a]	0.8957 ± 0.211[b]	0.9760 ± 0.285	1.0660 ± 0.139

Means ± SD are shown

[a] Significant when compared with healthy (control) men

[b] Significant when compared with healthy (control) women

Table 3 Numbers of osteopenic and osteoporotic subjects in groups

	Patients		Controls	
	Men	Women	Men	Women
Osteoporosis	5[a]	8[b]	0	0
Osteopenia	54[a]	48[b]	8	4

[a] Significant when compared with healthy (control) men

[b] Significant when compared with healthy (control) women

3). BMD was low in 54 men and 48 women of group 1. There was no statistically significant difference between BMD values of male and female patients in group 1. Significant differences in bone density were present when the whole groups were compared as well as when the males and females were compared separately (Table 2). ($P > 0.05$)

In group I, analysis of 24-h urine collections revealed that there were hypocitraturia, hyperoxaluria, hyperuricosuria, both hypocitraturia and hyperoxaluria and normal results in 23 (15.3%), 39 (26.0%), 9 (6.0%), 13 (8.7%) and 66 (44.0%) patients, respectively. In the control group, urinary analysis was normal. There were no significant differences in urine calcium (or volume, citrate, oxalate) between the male or female normocalciuric stone formers and the respective normal controls.

There was no statistically significant correlation between urinary analysis and low BMD ($P > 0.05$). It was determined that 120 (80.0%), 20 (13.3%) and 10 (6.7%) patients in group 1 had calcium oxalate, calcium phosphate and mixed calcium oxalate-calcium phosphate stones, respectively. When statistical comparisons were made between the two groups, it was determined that BMD was significantly low for total femur ($P < 0.05$); BMD, *T*-score and *Z*-score were significantly low for femur neck ($P < 0.001$) and for lumbar spine (L2–L4) ($P < 0.001$) in group 1 (Table 4).

The relationship between BMD reduction (osteoporosis and osteopenia) and 24-h urine results was not statistically significant ($P > 0.05$) (Tables 5, 6). It was found that while there was a statistically significant correlation between calcium oxalate stones and osteopenia ($P < 0.05$), no such correlation existed for other stone types (Fig. 1).

Table 4 BMD and *t* scores in groups

BMD (gr/cm^2)			
	Group 1 (BMD)	Group 2 (BMD)	*P*
Total femur	0.897 ± 0.132	0.945 ± 0.170	<0.05
Femur neck	0.759 ± 0.132	0.887 ± 0.135	<0.001
Lumbal Spine (L2–L4)	0.874 ± 0.130	1.021 ± 0.301	<0.001
t score			
	Group 1 (*t* score)	Group 2 (*t* score)	*P*
Total femur	−0.795 ± 0.689	−0.588 ± 2.416	>0.05
Femur neck	−0.883 ± 0.749	0.435 ± 0.547	<0.001
Lumbal spine (L2–L4)	−1.509 ± 1.224	−0.225 ± 0.854	<0.001

Means ± SD are shown

P values were calculated by unequal variance (Students's *t* tests)

Discussion

Urinary system stone disease is a multisystem disease. The most frequent extrarenal complication seen in patients with idiopathic calcium stone disease is spinal bone loss [19]. In the first study on the relationship between urolithiasis and bone mineral density, it was determined that bone mineral density was low [14]. After this study, the relationship between calcium metabolism and urolithiasis was investigated. Jaeger et al. [18] demonstrated that BMD was low in stone patients regardless of hypercalciuria.

Pietschmann et al. [20] determined that the rate of osteoporosis in hypercalciuric patients was 10% in a study comparing hypercalciuric and nonhypercalciuric patients. They attributed this rate to environmental factors, diet and high BMI. Pacifici et al. [15] showed that there was a correlation between interleukin-1 (IL-1) activity, a marker of bone destruction, and urinary calcium levels in osteoporotic men compared to nonhypercalciuric patients. Additionally, it was reported that

Table 5 Relationship between BMD results and 24-h urine analysis in Group 1 (Pearson's linear regression analysis)

	Normal urine analysis	Hyperoxaluria	Hypocitraturia	Hyperuricosuria	Hypocitraturia Hyperoxaluria	*p*
Osteoporosis	4 (%2.66)	4 (%2.66)	3 (%1.99)	-(%0)	2 (%1.34)	NS
Osteopenia	52(%34.66)	22 (%14.66)	15 (%9.99)	5 (%3.33)	8 (%5.33)	NS
Normal BMD	10(%6.66)	13 (%8.66)	5 (%3.33)	4 (%2.67)	3 (%1.99)	NS
Total	66 (%44)	39 (%26)	23 (%15.33)	9 (%6)	13 (%8.66)	

NS not significant

*Statistically significant ($P < 0.05$)

Table 6 Comparisons of blood biochemical values in groups

	Patients	Controls	*P*
Calcium (mg/dl)	6.47 ± 1.5	6.65 ± 1.4	NS
Uric acid (mg/dl)	4.2 ± 1.4	3.99 ± 1.1	NS
Creatinine (mg/dl)	0.8433 ± 0.15	0.8317 ± 0.19	NS
potassium (mEq/L)	4.25 ± 1.23	4.1 ± 1.1	NS
i PTH (pg/ml)	35.03 ± 8.35	37.57 ± 6.19	NS

NS not significant

Means ± SD are shown

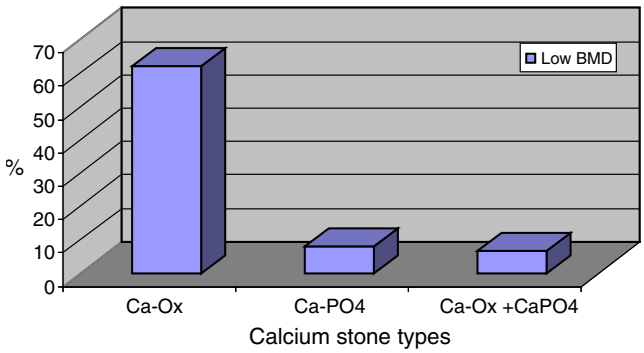

Fig. 1 Calcium stone types and low BMD rates

IL-1 levels were increased in hypercalciuric patients. In other studies, Betaille et al. and Fuss et al. [16, 17] reported that the rate of osteoporosis in hypercalciuric patients was 30 and 10 %, respectively. Trinchieri et al., in a study performed using DEXA, found that the rate of osteopenia and osteoporosis was 48 and 6% in hypercalciuric patients. They determined that BMD was lower in hypercalciuric patients (57%) than in normocalciuric patients (44%). In this study, WHO criteria were not used, but the patients were evaluated according to *Z*-score [21]. In a study performed according to WHO criteria, Caudarella et al. also determined osteoporosis and osteopenia in 10 and 43% of the patients, respectively. In another study, they reported that the rate of osteoporosis and osteopenia was 14 and 54%, respectively [22, 23].

According to our study of normocalciuric patients, the rate of low BMD was 76.7 and 20.0% in the patient group and healthy subjects, respectively. According to WHO criteria (*T*-score), there were osteoporosis and osteopenia in 13 (11.3%) patients and 102 (65.4%) patients, respectively, and there was osteopenia in 12 (20%) subjects of the control group. When the results of our study were evaluated, the rate of osteoporosis was similar to those reported from other studies of patients with urolithiasis, but the rate of low BMD was lower than the literature data.

The differences between rates of osteopenia and osteoporosis reported in these studies might originate from different methods of densitometric measurements (i.e. single photon absorptiometry, single X-ray and dual X-ray absorptiometry, quantitative computerized tomography) and from different regions of measurement (i.e. lumbar spine, hip, distal and ultra distal forearm).

Another important reason for the difference was that the prevelance of stone disease (14.8%) in our country was higher than that of the USA (2–8%) and of European countries (1–5%) [7]. When the demographic data and dietary habits (low calcium, high protein, high sodium diet) of stone patients in our country were taken into consideration, this high rate could be explained [24].

In a study of patients with urinary system stone disease, Tefekli et al. [24] reported that rates of low education status, high protein intake and high sodium intake were 58.2, 32.9 and 77.6%, respectively. In another study, Gur et al. [25] reported that there was a significant correlation between educational level and BMD. Although mechanisms of association between education level and low bone mineral density remained partly unexplained, this could be attributed to low calcium intake due to low socioeconomic level. The low BMD in our study could be attributed to general dietary habits of our population (low calcium and high protein diet). Sedentary lifestyle and low education level in stone patients could also cause this low BMD [24].

In normocalciuric subjects, who do not show metabolic alterations linked to excessive animal protein intake, bone mass loss appears to be less clear. Other factors may be involved in its pathogenesis, such as a low calcium and a high salt dietary intake, which are both able to reduce bone mass [18]. Stone-forming patients seem to have a higher susceptibility to a low calcium diet, which may be due to an excessive protein intake or to immunological disorders [26]. Asplin et al. have determined that stone formers consumed less calcium than non-stone formers [27]. Patients with kidney stones may follow reduced calcium diets to avoid recurrence, thus putting upon their bones an undue potential force for mineral loss.

All these observations suggest that a diet with normal calcium and proteins and low sodium content should be prescribed for patients with idiopathic calcium stone disease.

Conclusion

Our results showed a severe loss of bone mass in patients with urinary system normocalciuric calcium

stone disease. Thus, the necessary precautions concerning bone mass protection should be taken and the patients should be informed about this issue.

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