Bone pain in dialysis patients is not associated with bone mineral density but with serum concentration of small uremic toxins

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Abstract

Purpose: Abnormalities in bone mineral density (BMD) are frequent disorder in dialysis patients. In our study we checked if such clinical symptom as bone pain may be associated with BMD.

Patients and methods: The study was performed in 30 dialysis patients. They were divided according to declared or not declared bone pain in any localization. The group with bone pain (n=10) included 7 women and 3 men, age 57.4±16.2 years, dialysis vintage 19.3, 6.5-45.5 months. The group without bone pain (n=20) consisted of 11 women and 9 men, age 55.5±18.9 years, dialysis vintage 20.5, 6.3-59.6 months. BMD was assessed by dual-energy x-ray absorptiometry in femoral neck (N) and lumbar spine from the second to the fourth lumbar vertebra (L2-L4). Routine clinical and laboratory parameters were evaluated and compared in both groups.

Results: The group with bone pain had higher serum concentrations of phosphate (6.2±1.4 mg/dl vs 4.9±1.1 mg/dl, p=0.012) and urea (136.0±37.4 mg/dl vs 111.3±23.5 mg/dl, p=0.035) than the group without bone pain. After adjustment of results to gender, age and dialysis vintage these differences remained significant, additionally the group with bone pain had higher serum creatinine concentration than the group without bone pain (9.5±2.4 mg/dl vs 7.5±2.9 mg/dl, p=0.009). There were no statistically significant differences between groups in BMD measured in N and L2-L4.

Conclusion: Our results suggest that bone pain in dialysis patients is associated rather with serum concentration of small uremic toxins than with BMD.

Key words: bone mineral density, bone pain, dialysis, uremic toxins.

Introduction

Abnormalities in bone mineral density (BMD) are well known disorder in dialysis patients [1-7]. They are frequently accompanied by signs and symptoms (bone pain, bone fractures), which diminish quality of life in affected patients.

Although pain has been appreciated as a problem for end-stage renal disease patients for more than 20 years, few studies exist on this subject [8]. It was shown that pain is present in 21-50% of hemodialyzed patients and is the important determinant of their quality of life as well as is associated with depression [9,10]. Bone pain in the lower back, pelvis, rib cage areas, or long bones of upper and lower limbs, which is made worse by movement, is frequent complaint in uremia. The pain may come on gradually or fluctuate over a period of weeks, or it may develop suddenly, associated with bone fracture. In the study of Weisbord et al. [10] bone or joint pain was shown in at least 50% of cases and reached over 3 scores in Likert Scale Score, similarly like muscle cramps. According to questionnaire studies of Lichodziejewska-Niemierko [11] nephrologists in Poland suspect that pain is present in 4-7 dialyzed patients of every 10 patients, and 13.6% of nephrologists assume that 8-10 patients of 10 ones complain of pain. Moreover, 72.7% of nephrologists suspect that pain should be described by 4-7 scores in VAS 0-10 scale.

In our study we checked if in dialysis patients bone pain may be associated with BMD or other routinely evaluated parameters.

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Received 04.06.2007 Accepted 03.08.2007

***Table 1*. The demographic and clinical characteristics of examined patients with and without bone pain**

Parameter	Patients with bone pain (n=10)	Patients without bone pain (n=20)	p value
Gender	7 women, 3 men	11 women, 9 men	0.693
Age (years)	57.4±16.2	55.5±18.9	0.786
Dialysis modality	9 PD, 1 HD	17 PD, 3 HD	0.849
Dialysis vintage (months)	19.3 (6.5-45.5)	20.5 (6.3-59.6)	0.975

HD – hemodialysis; PD – peritoneal dialysis

***Table 2*. Results of bone mineral density (BMD) obtained in examined patients with and without bone pain**

Parameter	the group with bone pain	the group without bone pain	p value
Femoral neck			
BMD (g/cm^2)	0.830±0.172	0.806±0.139	0.681
T-score	-1.43 (-3.25-2.37)	-1.57 (-4.06-1.15)	0.315
BMD as % peak bone mass	87.6±23.3	80.0±15.7	0.297
Z-score	-0.65 (-2.36-2.97)	-0.77 (-2.36-2.01)	0.384
BMD as % age norm	97.6±24.3	90.4±14.5	0.328
Lumbar spine			
BMD (g/cm^2)	1.067±0.226	1.078±0.282	0.917
T-score	-0.33 (-3.95-1.73)	-1.25 (-3.13-4.07)	0.538
BMD as % peak bone mass	92.1±18.9	90.5±20.9	0.837
Z-score	0.54 (-4.41-2.14)	-0.73 (-1.85-4.49)	0.409
BMD as % age norm	100.2±24.3	95.5±19.5	0.577

Patients and methods

The study was performed in 30 stable patients in stage 5 of chronic kidney disease: 26 persons were treated with peritoneal dialysis (PD) and 4 – with hemodialysis (HD). The underlying disorders leading to end-stage renal failure were chronic tubulointerstitial nephritis (8 cases), diabetic nephropathy (7 cases), chronic glomerulonephritis (5 cases), polycystic kidney disease (4 cases), hypertensive nephropathy (1 case), obstructive nephropathy (1 case). In 4 cases a reason for end-stage renal disease remained unknown.

All patients were asked by the younger investigator about feeling pain in limbs, spine, pelvis, rib cage areas and their answers were evaluated and qualified by both investigators together with analysis of medical histories in order to check patients' pain complaints over time documented in the written form. Uremic patients, who declared bone pain at least 4 times and occurrence of pain was documented at least two times by a physician on routine visit during a year preceding the study, were included to the group of patients with bone pain.

Data on demographic and clinical characteristics of patients with bone pain and without it are presented in the *Tab. 1*.

BMD was examined by dual-energy x-ray absorptiometry (DEXA), which is a reference method to measure bone mass in various skeletal sites and to assess fracture risk [12]. Assessment of bone mass was performed in two sites: femoral neck – N and lumbar spine from the second to the fourth lumbar vertebra – L2-L4. Simultaneously the following parameters were evaluated: serum concentration of intact parathyroid hormone (iPTH), total calcium, ionized calcium, inorganic phosphate, urea, creatinine and uric acid, serum activity of total alkaline phosphatase, blood pH, serum markers of inflammation (C-reactive protein – CRP, ferritin), bioimpedance records of body composition (total body water, extracellular water, intracellular mass, lean body mass, fat body mass) as well as blood/ /serum parameters (hemoglobin, total protein, albumin, total cholesterol) and anthropometric markers (waist circumference, hip circumference, body mass index) of nutritional state. Laboratory markers were determined using standard methods.

Results are expressed as mean and one standard deviation, or as median and range. The distribution of variables was assessed using the Kolmogorov-Smirnow test. Serum concentrations of CRP and iPTH were not normally distributed in both groups. Patients with bone pain additionally did not show the normal distribution of total cholesterol, albumin and total alkaline phosphatase, whereas patients without bone pain did not have the normal distribution of total calcium, volume of extracellular water as well as T-score and Z-score for BMD in L2-L4.

The results were compared with adjustment for gender, age, dialysis modality and dialysis duration to eliminate their possible influences on significance of differences in evaluated variables as associated with bone pain. Our previous studies showed associations between BMD and both age and gender of examined patients [13]. In multiple regression analysis ANCOVA methodology was used. A p value below 0.05 was considered as statistically significant.

Results

The examined groups did not show significant differences (p values >0.05) in gender distribution, age, dialysis modality and dialysis vintage (*Tab. 1*).

BMD assessed in the femoral neck and the lumbar spine (L2-L4) was not statistically significant (p values >0.05) in the examined groups (*Tab. 2*).

***Figure 1*. Serum concentration of inorganic phosphate in dialyzed patients with and without bone pain**

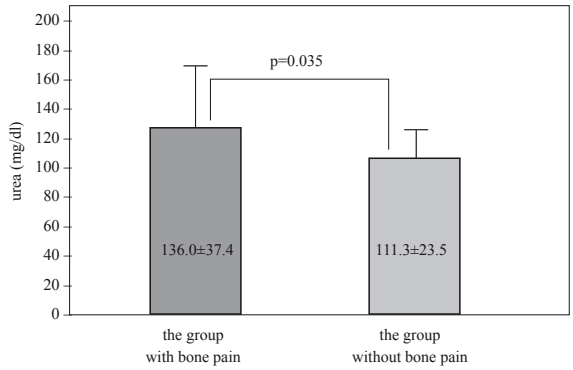


***Figure 2*. Serum concentration of urea in dialyzed patients with and without bone pain**

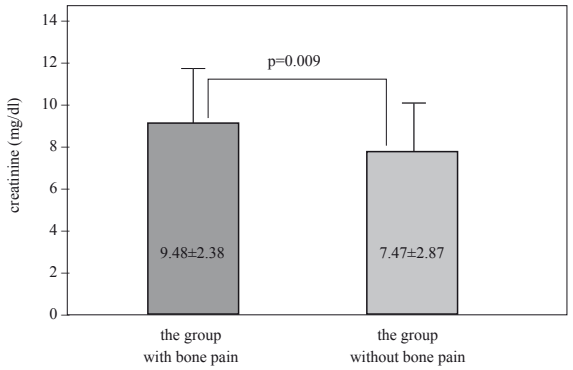
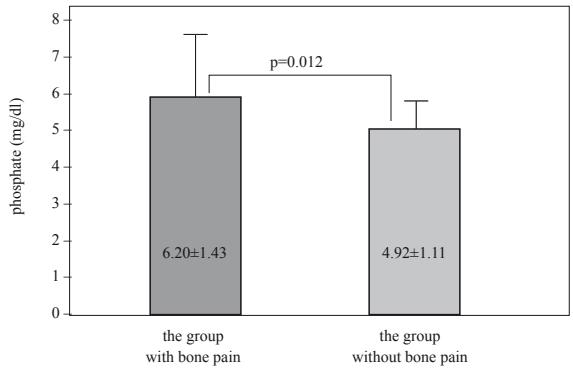


***Figure 3*. Serum concentration of creatinine in dialyzed patients with and without bone pain**



In univariate analysis, the group with bone pain had significantly higher serum concentrations of inorganic phosphate (p=0.012, *Fig. 1*) and urea (p=0.035, *Fig. 2*) than the group without bone pain. In multivariate analysis, after adjustment of results for gender, age and dialysis vintage these differences remained significant. Moreover, the group with bone pain revealed higher serum creatinine concentration than the group without bone pain (p=0.009, *Fig. 3*). Other examined parameters were not significantly different (p values >0.05) between both groups (*Tab. 3*).

Discussion

Pain is a subjective complaint, difficult for quantitative evaluation. Bone pain is usually attributed to bone disease, also to renal osteodystrophy [14] and osteoporosis [15,16]. The latter disorder may be successfully diagnosed by evaluation of bone mineral density (BMD) [12]. However, in our study, patients suffering from bone pain did not show significant differences in BMD. Moreover, also serum parameters closely related to

***Table 3*. Selected results obtained in examined patients with and without bone pain**

Parameter	Patients with bone pain	Patients without bone pain	p value
iPTH (pg/ml)	192 (14.9-1967)	242 (12.3-913)	0.660
Total calcium (mg/dl)	9.06±1.22	8.87±0.67	0.843
Ionized calcium (mg/dl)	4.19±0.79	4.32±0.53	0.625
ALP (IU/l)	82.8±47.1	83.7±27.9	0.235
Uric acid (mg/dl)	5.78±0.55	5.91±0.88	0.662
Blood pH	7.37±0.05	7.38±0.05	0.773
CRP (mg/l)	1.70 (0.00-10.46)	0.80 (0.00-12.20)	0.367
Ferritin (ng/ml)	366±220	369±249	0.977
TBW (l)	39.5±9.2	37.7±6.8	0.542
ECW (l)	17.1±3.6	16.7±4.6	0.644
ICW (l)	22.4±6.0	20.7±3.5	0.340
LBM (kg)	52.2±12.7	48.9±9.0	0.423
FBM (kg)	23.1±8.6	21.3±7.3	0.555
BMI (kg/m^2)	28.5±6.3	25.7±4.6	0.171
Waist circumference (cm)	98.1±14.7	95.8±12.2	0.656
Hip circumference (cm)	104±13	100±9	0.333
Hemoglobin (g/dl)	10.9±1.5	11.7±0.8	0.051
Total protein (g/l)	70.3±6.8	68.7±5.9	0.500
Albumin (g/l)	34.6±5.5	36.1±4.2	0.281
Total cholesterol (mg/dl)	208±55	212±43	0.823

ALP – alkaline phosphatase; BMI – body mass index; CRP – C-reactive protein; ECW – extracellular water; FBM – fat body mass; ICW – intracellular water; LBM – lean body mass; PTH – intact parathyroid hormone; TBW – total body water

bone metabolism (iPTH, total and ionized calcium, alkaline phosphatase) were not different between the examined groups.

Pain is one of the main components of inflammatory state. Laboratory markers of inflammation – increased serum concentrations of CRP and ferritin and decreased serum level of albumin – were similar in both groups. It may indicate that bone pain cannot be related to differences in expression in inflammatory state frequently seen in dialyzed patients [17-19].

Obese people frequently complain of pain in the lumbosacral spine, hips, knees, and ankles because obesity/overweight is frequently associated with joint pathology (osteoarthrosis), which leads not only to joint pain, but also to bone pain [20]. In our study, patients suffering from bone pain showed, however, similar anthropometric markers of nutritional state, bioimpedance records and laboratory indices of nutrition.

Uremic toxicity, evaluated by measurements of serum concentrations of small molecules (urea, creatinine, uric acid, phosphate), was more pronounced in dialysis patients who complained of bone pain. Our observation indicating association of bone pain and uremic toxicity is in agreement with results of Unruh et al. [21] showing that the high dose hemodialysis intervention was accompanied by significantly less pain in treated patients. Intensive HD treatment obviously caused lower uremic toxicity.

It cannot be excluded that patients with more advanced uremia are especially sensitive for pain signals, or such signals are released easier in the uremic environment. High or low serum concentrations of uremic solutes can be harmful. Serum level of inorganic phosphate is a factor related to bone metabolism, and also to less adequate dialysis treatment, like higher serum concentrations of urea and creatinine. Our patients with bone pain had higher serum level of phosphate than patients without it, but acute deficiency of phosphate also leads to bone pain [22]. Factors directly contributing to development of bone pain are not classified. Thus, we can only identify associations between serum concentrations of urea, creatinine and phosphate and bone pain, but causality cannot be confirmed.

Acknowledgement

The paper was presented at the 5th International Congress of the Uremic Research and Toxicity, Gdańsk/Sopot, 18-20.05.2007.

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