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BRIEF REPORT

Relative value of the lumbar spine and hip bone mineral density and bone turnover markers in men with ankylosing spondylitis

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Abstract The purpose of this study is to evaluate bone mineral density (BMD) and bone turnover markers in men with ankylosing spondylitis (AS) and to determine their relationship with clinical features and disease activity. Serum carboxi terminal cross-linked telopeptide of type I collagen (CTX), osteocalcin (OC) levels, and BMD of lumbar spine and proximal femur were evaluated in 44 males with AS, 18–60 years of age, and compared with those of 39 age-matched healthy men. Men with AS had a significantly lower BMD at the femoral neck and total hip as compared to age-matched controls (all $p<0.01$). Osteopaenia or osteoporosis was found in 59.5% AS patients at the lumbar spine and in 47.7% at the femoral neck. Mean serum levels of OC and CTX were similar in AS patients and controls. There were no significant differences in BMD and bone turnover markers when comparing subgroups stratified according to disease duration or presence of peripheral arthritis. No correlations were found between disease activity markers and BMD or OC and CTX. In a cohort of relatively young males with AS, we found a high incidence of osteopaenia and osteoporosis. Disease activity and duration did not show any significant influence on BMD or serum levels of OC and CTX.

Keywords Ankylosing spondylitis · Bone mineral density · C-terminal cross-linked telopeptide of type I collagen · Osteocalcin · Osteoporosis

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Introduction

Structural damage in ankylosing spondylitis (AS) is characterised by osteoproliferation leading to development of syndesmophytes, regarded as the hallmark of the disease. Besides excessive bone formation, AS is characterised by bone loss leading to osteoporosis and increased risk of vertebral fractures. There are still several controversial issues concerning osteoporosis in AS, for instance its prevalence, distribution, severity and pathogenesis [1]. Bone turnover markers provide a dynamic assessment of bone quality that cannot be done by measuring bone mineral density (BMD) [2]. There are only a few studies in recent literature that have analysed bone turnover markers in male patients with AS and yielded conflicting results. Osteocalcin is considered to be a very sensitive and specific bone formation marker with proven utility for the assessment of bone turnover in active rheumatoid arthritis [3]. Serum carboxy terminal telopeptide of type I collagen (CTX) was chosen for assessing bone resorption due to its higher specificity and lower variability as compared to other resorption markers [4].

The aim of this study was to evaluate BMD and levels of osteocalcin and serum CTX in men with AS and investigate their association with disease duration, disease activity and clinical features of AS.

Patients and methods

Patients

In this cross-sectional study, 44 men with AS in all stages of the disease were enrolled. They attended the Rheumatology Department at the University of Medicine and Pharmacy Cluj Napoca, Romania, between January 2009 and June 2009, as inpatients or outpatients. Eligible participants were Caucasian males, 18–60 years of age with a diagnosis of primary AS according to the modified New York criteria [5] that consented to take part in the study, as approved by the local ethic committee. We decided to include only men with age less than 60 years in order to eliminate potential confounding factors on bone, such as age and menopause. We excluded subjects with any condition or treatment that might affect bone metabolism. The control group corresponded to 39 age-matched healthy men.

With 40 cases in each group, this study had 80% power to detect the difference in the prevalence of osteoporosis in AS patients and healthy subjects with an odds ratio (OR) of 3, using a 95% confidence interval (95% CI). For the calculation of the target sample size, we have assumed that the prevalence of osteoporosis in AS patients and in controls is 36% and 10%, respectively.

Clinical and radiological assessments

Demographic and clinical variables were recorded by anamnesis and clinical examination. The patient's disease activity and function were evaluated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [6] and Bath Ankylosing Spondylitis Function Index (BASFI) [7] respectively. Sacroiliac, anteroposterior and lateral dorsolumbar spine radiographs were examined for grading the sacroiliitis and for the assessment of syndesmophytes.

BMD assessments

BMD was measured at the posteroanterior lumbar spine (L1-L4), femoral neck, and total hip by dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy Advance (GE Healthcare, USA). All BMD measurements were made on the same densitometer at a single centre (Centre of Osteoarthrology "Osart" Cluj Napoca, Romania). The coefficient of variation for the Lunar phantom was 0.7%. According to the WHO criteria, osteopaenia was defined as T score between −1 and −2.5 and osteoporosis as a T score below −2.5 (8).

Biochemical assessments

Blood samples were collected in the morning between 8:00 and 10:00 AM after an overnight fast, and then stored at −80°C. The frozen aliquots of serum were shipped on dry ice to the Department of Clinical Analysis from University Hospital "Reina Sofia" Córdoba, Spain where analysis of biomarkers of bone metabolism were done. Serum levels of N-Mid osteocalcin (OC) and carboxi terminal CTX were assayed by electrochemiluminescence immunoassays (ECLIA) using commercially available kits (N-Mid osteocalcin ECLIA and β-CrossLaps ECLIA). The intra-assay and inter-assay coefficients of variation were below 10% for all parameters. Disease activity in AS patients was assessed by the C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) was performed at the local laboratory.

Statistical analysis

The statistical programme SPSS for Windows, version 15.0 was used for all analysis. Results were expressed as mean (standard deviation) or number (percentage). The Student's t test or the Mann–Whitney U test was used to assess differences between the AS patients and controls, and between subgroups of AS patients. Proportions were compared between groups by using chi-squared test or Fisher's exact test. The correlation between variables was analysed using Pearson's correlation test. The level of statistical significance was <0.05 (two-tailed).

Results

The clinical, radiographic and laboratory characteristics of patients with AS are summarised in Table 1.

The femoral neck BMD and total hip BMD were significantly lower in men with AS compared to controls (both $p<0.01$; Table 2). Lumbar spine BMD was also lower in the AS group, although the difference did not reach significance ($p=0.06$; Table 2).

According to the WHO classification, nine patients (21.4%) were osteoporotic at the femoral neck and 16 (38.1%) were osteopaenic. At the lumbar spine, 11 patients (25%) were osteoporotic while ten (22.7%) were osteopaenic. Significantly, more men with AS were osteopaenic or osteoporotic at the femoral neck as compared with controls (AS vs controls, 59.5% vs 25.6%, $p=0.001$). Osteopaenia or osteoporosis at the lumbar spine was found more frequent in AS patients than in controls, although not statistically significant (AS vs controls, 47.7% vs 35.9%, $p=0.08$).

The serum levels of OC were in the normal range without difference between AS and controls. The serum levels of CTX were higher in AS patients as compared with controls, but the difference did not reach statistical significance ($p=0.08$; Table 2).

Table 1 Clinical, radiographic and laboratory characteristics of patients with ankylosing spondylitis (n=44)

Age, years	41 (10.2)
Disease duration, years	13.3 (8.9)
Peripheral arthritis, *n* (%)	25 (56.8)
Coxitis, *n* (%)	11 (25)
Uveitis, *n* (%)	12 (27.3)
Schober's index, cm	1.9 (1.6)
Chest expansion, cm	2.5 (1.5)
Occiput-to-wall distance, cm	5.5 (6.5)
Sacroiliitis, *n* (%)	
Grade 2	14 (31.8)
Grade 3 or 4	30 (68.2)
Syndesmophytes, *n* (%)	20 (45.5)
ESR, mm/h	30.3 (25.7)
CRP, mg/dl	1.5 (1.4)
BASDAI	6.8 (2)
BASFI	6.4 (2.2)

Data presented as mean (standard deviation) or numbers (percentage) of patients.

Table 2 Demographic characteristics, bone mineral density and bone turnover markers in patients with ankylosing spondylitis and controls

Characteristics	AS(n=44)	Controls(n=39)	P[a]
Demographic variables			
Age, years	41 (10.2)	39.5 (9.3)	0.47
Weight, kg	73.7 (14.9)	83.9 (12.1)	0.001
Height, cm	171.3 (7)	178.9 (6)	<0.001
BMI, kg/m^2	25 (4.5)	26.2 (3.9)	0.19
DXA measurements			
Lumbar spine L1-L4			
BMD, g/cm^2	1.08 (0.2)	1.16 (0.2)	0.06
T score	−1.2 (1.8)	−0.42 (1.4)	0.04
Left femoral neck[b]			
BMD, g/cm^2	0.90 (1.6)	1.03 (0.2)	0.001
T score	−1.3 (1.3)	−0.25 (1.2)	<0.001
Left hip[b]			
BMD, g/cm^2	0.94 (1.8)	1.05 (0.1)	0.001
T score	−1.1 (1.2)	−0.27 (1)	0.001
Bone turnover markers			
OC, ng/ml	24.4 (9.9)	23 (10.2)	0.55
CTX, ng/ml	0.56 (0.9)	0.30 (0.1)	0.08

Results are given as mean (SD)

BMI body mass index, *T score* standard deviation below peak bone mass, *Z score* standard deviation below the mean BMD for people of the same age

[a] Comparison between AS patients and controls, Student's *t* test

[b] Two AS patients were excluded from the proximal femur analysis due to bilateral hip prosthesis

Comparison between AS subgroups

The BMD values were similar in AS patients group with disease duration >10 years (n=21) when compared with patients with disease duration ≤10 years (n=23). Patients with longer disease tended to have higher levels of CTX than patients with disease duration ≤10 years, although the difference did not reach significance [0.76 (1.3) vs 0.33 ng/ml (0.1); p=0.13].

AS patients with syndesmophytes (n=20) had a significantly higher spine BMD than patients without syndesmophytes (n=24) [1.15 (0.2) vs 1.02 g/cm^2 (0.2); p=0.03]. Bone turnover markers were similar in both groups (all p>0.05).

The BMD values and serum levels of OC and CTX were similar in AS patients with peripheral joint involvement when compared to axial disease. Similarly, we did not find any difference in BMD values when we analysed the same cohort from the point of view of disease activity as expressed by elevated levels of CRP>0.6 mg/dl (all p> 0.05). Mean CTX values were higher in AS patients with elevated CRP as compared with patients with normal CRP, although the difference was not statistically significant [0.70 (1.2) vs 0.34 ng/ml (0.1), p=0.21].

Correlations between BMD values, bone turnover markers and clinical and disease activity parameters

The BMD at the femoral neck was positively correlated with Schober's test (r=0.41, p=0.007) and negatively correlated with BASFI (r=−0.38, p=0.02). We found no correlation between the spine BMD and clinical parameter, including demographic variables, spine mobility values, peripheral arthritis and BASFI. Disease duration was not correlated with clinical parameters, BMD or serum levels of the studied bone markers (all p>0.05). A mild correlation was found between lumbar spine BMD and age (r=0.30, p=0.04).

No correlation was found between OC or CTX levels and CRP levels (r=−0.03, p=0.84 and r=0.09, p=0.55, respectively) or BASDAI score (r=0.23, p=0.13 and r=−0.6, p= 0.70, respectively). Also, serum levels of OC and CTX did not correlate with any of the clinical parameters or BMD values. We found no correlation between BMD at any site and parameters of disease activity (ESR, CRP or BASDAI) (data not shown, all p>0.05).

Discussion

In a specifically male population, we found that AS patients had a lower femoral neck and total hip BMD than controls. In contrast, the lumbar spine BMD was not significantly different from the control group. In our study, patients with syndesmophytes had a significantly higher lumbar spine

BMD than patients without syndesmophytes. Several studies in the recent literature in the field have documented low bone mass in the spine and hips of AS patients, with notable differences according to the stage of the disease. In a cross-sectional study, Donelly et al. [9] also found that lumbar spine BMD was decreased only in patients with mild AS, results confirmed by other researchers [10, 11]. Based on previous research, as well as on the results of the present study, we may conclude that the presence of syndesmophytes could jeopardise an appropriate assessment of bone loss using posteroanterior lumbar spine DXA. DXA at the femoral neck is considered the most sensitive method for evaluation of osteoporosis even in AS patients without syndesmophytes [12].

In this cohort, a high prevalence of osteopaenia (22.7% at the lumbar spine and 38.1% at the femoral neck) and osteoporosis (25% at the lumbar spine and 21.4% at the femoral neck) was observed. These data are consistent with previous reported prevalence of osteoporosis in AS patients that vary from 18.7% to 62% [13].

The lack of correlation between BMD and disease duration observed in our cohort agrees with some previous studies and suggests that bone loss occurs early in the disease [14, 15]. Longitudinal studies had demonstrated a clear relationship between bone loss and markers of disease activity in AS [16, 17]. As in previous cross-sectional studies, we did not find correlations between BMD at any measurement site and disease activity parameters [14, 15].

We evaluated bone formation by serum OC and we found no difference between AS patients and controls. Moreover, we were not able to show any correlation between OC serum levels and markers of disease activity (ESR, CRP and BASDAI) or BMD values. In line with our study, other authors have found normal OC values in AS, which were not correlated to the ESR or CRP levels [18, 19].

Several researchers have evaluated different markers of bone resorption, including urinary excretion of pyridinoline (PYD) and deoxypyridinoline (DPD), amino terminal cross-linked telopeptide of type I collagen (NTX) and CTX, and found no difference between AS patients and controls [18–20]. In contrast, other studies reported elevated levels of NTX, CTX, PYD and DPD, which were correlated with several markers of disease activity and severity [21–23]. In our study, the mean CTX serum levels in AS patients tended to be higher than in the control group, although the difference was not statistically significant. Similarly, in subgroup analyses, we have noticed the same trend even in AS patients with more active disease (as assessed by CRP levels) and more severe disease (indicated by the presence of syndesmophytes) when compared with inactive and milder disease. Our study failed to show a correlation between serum CTX levels and markers of disease activity.

To conclude, our results suggest that osteoporosis is a common condition among men with AS. Bone loss occurs early in the disease and its progression is better assessed by using DXA at the femoral neck. In our study, BMD values are better correlated with cumulative damage than with disease activity, suggesting that the mechanisms involved in bone loss may differ according to disease stages. Patients with active and severe AS tend to have increased levels of CTX, although our study has not been able to show a relationship between bone turnover markers and disease activity parameters.

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Disclosures None

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