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Bone Mineral Density in Patients with Ankylosing Spondylitis: Incidence and Correlation with Demographic and Clinical Variables

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Abstract: *Objective*: To evaluate bone mineral density (BMD) in patients with ankylosing spondylitis (AS) and determine its correlation with the demographic and clinical characteristics of AS. *Patients and Methods*: Demographic, clinical and osteodensitometric data were evaluated in a cross-sectional study that included 136 patients with AS. Spine and hip BMD were measured by means of dual energy X-ray absorptiometry (DXA). Using the modified Schober's test we assessed spine mobility. We examined the sacroiliac, anteroposterior and lateral dorso-lumbar spine radiographs in order to grade sacroiliitis and assess syndesmophytes. Disease activity was evaluated using C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). Demographic data and BMD measurements were compared with those of 167 age- and sex-matched healthy controls. *Results*: Patients with AS had a significantly lower BMD at the spine, femoral neck, trochanter and total hip as compared to age-matched controls (all $p<0.01$). According to the WHO classification, osteoporosis was present in 20.6% of the AS patients at the lumbar spine and in 14.6% at the femoral neck. There were no significant differences in BMD when comparing men and women with AS, except for trochanter BMD that was lower in female patients. No correlations were found between disease activity markers (ESR, CRP) and BMD. Femoral neck BMD was correlated with disease duration, Schober's test and sacroiliitis grade. *Conclusion*: Patients with AS have a lower spine and hip BMD as compared to age- and sex-matched controls. Bone loss at the femoral neck is associated with disease duration and more severe AS.

Keywords: Ankylosing spondylitis; Bone mineral density; Osteoporosis.

Introduction

Bone loss is now a widely acknowledged characteristic of many inflammatory rheumatic diseases [1]. Within the range of chronic inflammatory arthritis, ankylosing spondylitis (AS) - the prototypical disease of the seronegative spondyloarthropathies - raises the dilemma of a disease characterized by new bone formation occurring in parallel with a process of bone loss [2]. The disease predominantly affects young males and is associated with progressive functional impairment, increased work disability and decreased quality of life [3].

Recent studies have shown that patients with ankylosing spondylitis display a high prevalence of OP and run a higher risk for fragility fractures [4]. However, the prevalence, distribution, severity and pathogenesis of osteoporosis in AS is still under debate. There are several factors possibly

involved in bone loss in rheumatic diseases, including reduced mobility due to functional impairment, adverse effects of some therapeutic agents, genetic factors, hormonal abnormalities and uncontrolled disease activity [5].

In spite of the difficulties in assessing bone mineral density (BMD) due to progressive emergence of syndesmophytes, dual energy X-ray absorptiometry (DXA) is considered the best method for diagnosing osteoporosis in AS patients [6].

The main objective of the present study was to evaluate bone mineral density (BMD) in ankylosing spondylitis patients, exploring the overall and subgroup incidence of reduced bone mass. The bone mineral density data from AS patients were compared with the data from a healthy age- and sex-matched population. We also evaluated the relationships between BMD and demographic and disease variables.

Material and Method

Patients and Methods

In this cross-sectional study, 136 patients with AS in all stages of the disease were enrolled. They were selected from regular attendees of the Rheumatology Department with the University of Medicine and Pharmacy Cluj-Napoca, Romania. All patients had a primary AS diagnosis according to the modified New York criteria [7]. We excluded subjects with any condition or treatment that might have affected bone metabolism (malabsorption, chronic renal and liver diseases, thyroid diseases, alcoholism, corticosteroids, anticonvulsants) and patients with other forms of spondyloarthropathy.

The control group consisted of 167 age- and sex-matched healthy subjects without a history of inflammatory rheumatic disease, conditions or medication responsible for bone loss.

Demographic and clinical variables were recorded, including age, weight, height, body mass index (BMI = Weight/Height^2, kg/m^2), disease duration, peripheral arthritis, coxitis and uveitis. Disease duration was defined as the time elapsed between the onset of the specific disease manifestations and enrolment in the study. Spine mobility was assessed using the modified Schober's test. We have also recorded the patients' medication history including intermittent or continuous use of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying drugs (DMARDs) and tumour necrosis factor-alpha (TNFα) blockers (Infliximab, Etanercept and Adalimumab). Sacroiliac, anteroposterior and lateral dorso-lumbar spine radiographs were examined in order to grade the sacroiliitis (according to New York criteria) and assess the syndesmophytes.

Bone mineral density (BMD) was measured at the postero-anterior (PA) lumbar spine (L2-L4), femoral neck, and total hip by means of dual energy X-ray absorptiometry (DXA), using a Lunar Prodigy Advance (GE Healthcare, USA). The same densitometer of the same centre (Centre of Osteoarthrology "Osart" Cluj Napoca, Romania) was used for all BMD measurements. Results were expressed as BMD in g/cm^2, and also as T-score (standard deviation from peak adult BMD) and Z-score (standard deviation from age-matched BMD). According to the WHO criteria, osteopenia was defined as T-score between -1 and -2,5 and osteoporosis as a T-score below -2,5 [8].

Statistical Analysis

The statistical programs Epi-Info 6 and SPSS were used for statistical analysis. Results were expressed as mean (standard deviation), or number (percentage). The Student's t-test was used to compare continuous variables between AS patients and controls, and between subgroups of AS patients. The chi-square test for the categorical variables or the Kruskal-Wallis test was performed when appropriate. The correlations between variables were presented as the Spearman's correlation coefficient (rho). The level of statistical significance was < 0.05 (2-tailed).

Results

The demographic, clinical, radiological and laboratory characteristics of the patient group are listed in table 1. Ninety-eight per cent of the patients were receiving intermittent or continuous treatment with NSAIDs and 78% of the patients were also treated with at least one disease-modifying drug (sulphasalazine, methotrexate and leflunomide). Ten patients were given a blocker of tumour necrosis factor α (Infliximab, Etanercept and Adalimumab).

Table 1. Clinical, radiological and laboratory characteristics of patients with ankylosing spondylitis (n =136)

Variables	Mean (SD) or n (%)	Median (range)
Age (years)	45.7 (14.0)	46.3 (21.4 – 86.7)
Male/Female [n (%)]	99 (72,8)/37 (27.2)	
Disease duration (years), (n = 132)*	14.3 (10.1)	12 (6 months – 44 years)
Peripheral arthritis [n (%)], (n = 127)*	66 (52)	
Coxitis [n (%)], (n =132)*	20 (15.2)	
Uveitis [n (%)], (n = 125)*	33 (26.4)	
Schober's test (cm), (n = 126)*	2.2 (1.7)	2 (0 - 6)
Sacroiliitis: grade 2, [n (%)] grade 3 or 4	48 (35.3) 88 (64.7)	
Syndesmophytes [n (%)], (n = 115)*	45 (39.1)	
ESR (mm/hour), (n = 122)*	34.8 (28.7)	28 (2-120)
CRP (mg/dl), (n = 115) *	1.7 (2.4)	1 (0-16)

Data presented as mean (standard deviation), median (range: min-max) or numbers (percentage) of patients
*Number of patients varies from 136 due to missing data
BMI: body mass index; ESR: erythrocyte sedimentation rate;
CRP: C-reactive protein; DMARDs: disease-modifying drugs

The healthy control subjects were age- and sex-matched to the patients with AS (Table 2). Patients with AS displayed a significantly lower weight and height than the subjects in the control group, but BMI was similar in both groups ($p = 0.11$; Table 2).

The femoral neck BMD and total hip BMD were lower in patients with AS as compared to controls, and the differences were highly significant (both $p < 0.0001$; Table 2). Similar results were observed for T- and Z-score of the neck and total hip. Lumbar spine BMD was significantly lower in the AS group as compared to healthy controls. The corresponding T- and Z-score were also decreased in AS patients, although the difference did not reach significance (both $p > 0.10$; Table 2).

According to the WHO classification for the lumbar spine BMD, 28 (20.6%) AS patients were osteoporotic and 45 (33.1%) were osteopenic (controls: 1.8% and 37.4%, respectively). At the femoral neck and total hip, 19 patients (14.6%) and 12 (9.2%), respectively were osteoporotic (controls: 1.2% at both sites). In addition, 58 (44.6%) patients were osteopenic at the femoral neck and 54 (41.5%) at the total hip. Significantly more patients with AS were osteopenic at the total hip or osteoporotic at the lumbar spine, femoral neck and total hip ($p < 0.001$).

The study included 37 women with AS, (16 pre-menopausal and 21 postmenopausal), with the mean age of 47.7 (12.5) years. The demographic variables (age, weight, BMI, menopausal status) were similar in the case of the women with AS and those from the control group. In the pre-menopausal group, BMD at any measured site were similar between women with AS and controls, except the trochanter BMD (AS vs. controls: [0.75 (0.1)] vs. [0.84 (0.1)] g/cm^2; $p = 0.01$). In contrast, postmenopausal women with AS had a significantly lower BMD at the femoral neck, trochanter and total hip as compared to controls (all $p < 0.01$). There was no significant difference between the 2 groups at the lumbar spine (postmenopausal women with AS vs. controls: [1.05 (0.2)] vs. [1.10 (0.2)] g/cm^2; $p = 0.35$).

Table 2. Comparative demographic and osteodensitometric variables of ankylosing spondylitis (AS) patients and controls[a]

	AS (n = 136)	Controls (n = 167)	P[b]
Demographic varibles			
Age (years)	45.7 (14.0)	46.9 (12.9)	0.44
Sex [%, (95% CI)]			
Males	72.8 (64.5 – 80.1)	61.7 (53.8 – 69.1)	NS[c]
Females	27.2 (19.9 -35.5)	38.3 (30.9 – 46.2)	
Weight (kg)	71.7 (14.7)	76.6 (15.3)	0.005
Height (cm)	167.9 (9.3)	170.5 (10.0)	0.02
BMI (kg/m^2)	25.4 (4.8)	26.3 (4.8)	0.11
DXA variables			
L2-L4 BMD (g/cm^2)	1.109 (0.21)	1.167 (0.17)	0.04
T-score L2-L4	-1.0 (1.7)	-0.9 (1.5)	0.44
Z-score L2-L4	-0.9 (1.8)	-0.4 (1.5)	0.11
Left femoral neck BMD (g/cm^2)	0.911 (0.16)	0.986 (0.16)	< 0.0001
T-score femoral neck	-1.1 (1.2)	-0.5 (1.2)	< 0.0001
Z-score femoral neck	-0.7 (1.8)	0.1 (1.0)	< 0.0001
Trochanter BMD(g/cm^2)	0.769 (0.15)	0.842 (0.14)	< 0.0001
T-score trochanter	-1.2 (1.3)	0.5 (1.1)	< 0.0001
Z-score trochanter	-0.9 (1.3)	-0.1 (1.1)	< 0.0001
Total hip (g/cm^2)	0.938 (0.16)	1.026 (0.15)	< 0.0001
T-score total hip	-0.9 (1.1)	-0.3 (1.0)	< 0.0001
Z-score total hip	-0.6 (1.2)	0.1 (1.1)	< 0.0001

[a] Data presented as mean (standard deviation), except where noted otherwise
[b] Student's t-test
[c] Overlap of the 95% CI of the frequency was considered to be not significant (NS)
BMI: body mass index; DXA: dual energy X-ray absorptiometry; BMD: bone mineral density;
T-score: standard deviation below peak bone mass; Z-score: standard deviation below the mean BMD for people of the same age

Ninety-nine men with mean disease duration of 44.9 (13.0) years and mean disease duration of 14.1 (9.8) years were compared to 103 age-matched healthy men. Men with AS displayed a significantly lower weight [AS vs. controls: 73.1 (14.1) vs. 81.2 (13.7) kg; $p < 0.0001$] and height [AS vs. controls: 171.2 (7.5) vs. 176.1 (13.7) cm; $p < 0.0001$] than subjects in the control group. The lumbar spine, femoral neck, trochanter and total hip BMD were significantly lower in men with AS as compared with the controls (all $p < 0.01$).

Table 3 illustrates the comparison between males and females in the study group. Females with AS had a significantly lower weight, height and BMI as compared with males patients. Both sexes were well matched in terms of age and disease duration, but differed with regard to disease severity. Male patients displayed notably reduced spine mobility and a more severe sacroiliitis. They also had a more active disease, as illustrated by the increased occurrence of peripheral joint involvement and higher CRP values as compared to female patients. BMD at the lumbar spine, femoral neck and total hip were similar in women and men with AS ($p > 0.05$). In contrast, trochanter BMD was significantly lower in female patients with AS as compared to male patients ($p = 0.002$, Table 3). Men with AS were more likely to suffer from osteoporosis than the females but the difference were not statistically significant [28.3% (19.7-38.2)] vs. [24.3% (11.8-41.2)].

There was a mild positive correlation between weight and bone density measured at any site (rho ranging from 0.25 to 0.39; all $p < 0.01$). Also, BMI was correlated with the lumbar spine, trochanter and total hip BMD, but not with the femoral neck BMD. There was a significant negative correlation between disease duration and BMD at the femoral neck and total hip (rho = - 0.28, and rho = - 0.21, respectively; both $p < 0.01$). There was no correlation between the lumbar spine BMD and disease duration. Only femoral neck BMD was correlated with age (rho = -0.21, $p = 0.02$). Also, femoral neck BMD was correlated with Schober's test (rho = 0.28, $p < 0.01$) and sacroiliitis grade (rho = - 0.19, $p < 0.05$), while lumbar spine BMD was not. We found no correlation between BMD at any site and disease activity parameters (ESR, CRP or BASDAI) (all $p > 0.05$).

Table 3. Demographic, clinical, radiological and laboratory characteristics of women and men with ankylosing spondylitis (AS)

Variables	Women with SA		Men with SA		p
	n*	Mean (SD) or n (%)	n*	Mean (SD) or n (%)	
Demographic varibles					
Age (years)	37	47.7 (12.5)	99	44.9 (13.0)	0.26[a]
Weight (kg)	37	68.1 (15.9)	99	73.1 (14.1)	0.08[a]
Height (cm)	37	159.1 (7.8)	99	171,2 (7,5)	< 0.0001[a]
BMI (kg/m^2)	37	26.9 (5.5)	99	24.9 (4.4)	0.03[a]
Disease variables					
Disease duration (years)	35	5.1 (11.0)	97	14.1 (9.8)	0.60[a]
Peripheral arthritis [n (%)]	34	8 (23.5)	93	40 (43.0)	0.002[b]
Coxitis [n (%)]	35	3 (8.6)	97	17 (17.5)	0.32[b]
Uveitis [n (%)]	34	9 (26.5)	91	24 (26.4)	0.82[b]
Schober's test (cm)	34	3.1 (1.9)	92	1.9 (1.6)	0.001[a]
Sacroiliitis grade [median (range)]	37	2 (2-4)	99	3 (2-4)	0.02[b]
Syndesmophytes [n (%)]	28	7 (25)	87	38 (43.7)	0.12[b]
ESR (mm/hour)	34	35.7 (27.7)	88	34.4 (29.2)	0.82[a]
CRP (mg/dl)	32	1.4 (3.0)	82	1.8 (2.1)	0.03[c]
DXA variables					
Lumbar spine BMD (g/cm^2)	37	1.09 (0.2)	99	1.11 (0.2)	0.60[a]
Left femoral neck (g/cm^2)	37	0.88 (0.2)	93	0.92 (0.2)	0.18[a]
Trochanter BMD (g/cm^2)	37	0.71 (0.1)	93	0.79 (0.2)	0.002[a]
Total hip (g/cm^2)	37	0.90 (0.1)	93	0.95 (0.2)	0.08[a]

Data presented as mean (standard deviation) except where noted otherwise

[a] Student's t-test

[b] χ^2 test

[c] Mann-Whitney U test

*Number of patients varies from n = 37 females and n = 99 males due to missing data

BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DXA: dual energy X-ray absorptiometry; BMD: bone mineral density.

Discussion

The results of the cross-sectional study exploring the BMD at different measurement sites and the incidence of reduced BMD revealed that patients with AS had lower bone mass than healthy age- and sex-matched controls. Further analysis demonstrated that femoral neck BMD was correlated with demographic and disease variables that reflected the cumulative damage of AS. In contrast, no correlation was found between BMD at any site and disease activity variables.

Our results agreed with previous studies that demonstrated lower BMD in AS patients [9-11]. Bone loss was noticeable early in the course of the disease, at all measurement sites. In contrast, lumbar spine BMD values were similar or even increased in AS patients with advanced disease, as compared to controls. It was suggested that in late AS, the presence of syndesmophytes could falsely elevate the spine BMD values [9,10]. In contrast to the aforementioned studies, we did not find a significant increase in bone mass at the lumbar spine. This might be explained by the heterogeneity of the studied population, since we have included AS patients in all stages of the disease, and more than half of the patients did not have syndesmophytes. In a recent study on a cohort of 103 patients with AS, Karberg et al [12] reported that bone loss was more frequently detected in AS patients with syndesmophytes, suggesting that bone growth and bone loss occurred in parallel. Their conclusion was that "the method of bone density measurement is critical and should be different depending on disease duration". It was established that DEXA at the femoral neck was the most sensitive method for evaluating OP in AS, even in patients without syndesmophytes.

The WHO criteria for the OP diagnosis have been validated for postmenopausal white women, while AS is a systemic disease mainly affecting male subjects. However, fracture risk is associated with a T score less than -2.5 SD in both sexes, and therefore it is reasonable to accept this

classification in the absence of validated values in AS patients. In our study, we found an increased prevalence of osteoporosis at the lumbar spine and femoral neck (20.6% and 14.6%, respectively). These results were consistent with the reported prevalence of osteoporosis in AS varying from 18.7% to 62% [4].

Our study confirmed the presence of a significant bone loss at the proximal femur (femoral neck, trochanter, total hip) only in postmenopausal women. In our patients, pre-menopausal women had a small, but significant decrease of trochanter BMD. We had also shown that women with AS at any age had similar spine BMD values with controls, results that agreed with previous studies. Juanola et al. [13] did not find significant variation in BMD values between pre-menopausal women with AS and controls. In contrast, in Speden's report, which included 66 women with AS, both pre-and postmenopausal patients had a significantly lower BMD at the proximal femur, as compared to their age and sex-matched controls [14].

The present study also demonstrated a consistent, statistically significant BMD decrease at all measurement sites in males with AS, as compared to age-matched healthy controls. In contrast, Franck et al. [15], examining 190 males with AS, had demonstrated a significant BMD reduction in AS patients' group only in the femoral neck and total hip.

The differences between males and females with AS have been examined by several researches and the results they yielded were quite conflicting. Some researchers found that male patients were prone to both more severe disease and osteoporosis [9,16], while others could not find any difference between BMD values of men and women [10,11]. In our study, BMD values were similar in case of both men and women, except for trochanter BMD. When applying the WHO criteria, we could not find any significant difference in what concerned the incidence of osteoporosis in men and women with AS. Our results therefore suggested that AS eliminates the relative protection of male patients against osteoporosis.

We found a significant negative correlation between disease duration and BMD at the femoral neck and total hip. Similarly, Toussirot et al. [17], who worked on a cohort of 71 patients with early disease, showed that only the femoral neck was correlated with disease duration. In addition, Capaci et al. [11] demonstrated a significant positive correlation between disease duration and lumbar spine BMD. The lack of correlation between BMD at any site and disease activity parameters (ESR, CRP) agreed with some previous studies [17], whereas it was in contrast with several others [18]. However, in a cross sectional study it is difficult to establish a correlation between a biological marker measured at a given point and BMD, which is a parameter reflecting the cumulative influence of the disease [2]. In the present study, femoral neck BMD was correlated with parameters reflecting the cumulative damage of AS (Schober's test, sacroiliitis grade), not with markers of disease activity. The results suggested that bone loss in AS may involve different mechanisms at different stages of the disease.

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