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ORIGINAL ARTICLE

Clinical significance of bone mineral density in Ankylosing Spondylitis patients: Relation to disease activity and physical function

Safaa Sayed [a,*], **Hanan Darweesh** [b], **Khaled Fathy** [b], **Abdel Moneim Mourad** [c]

[a] *Rheumatology Department, Cairo University, Egypt*
[b] *Internal Medicine Department, Ain Shams University, Egypt*
[c] *Radiology Department, Assuit University, Egypt*

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Abstract *Aim of the work:* The aim of this work was to assess the bone mineral density (BMD) in Ankylosing Spondylitis (AS) patients and to investigate its relation with clinical and laboratory parameters, imaging of sacroiliac joints, disease activity and physical function.

Patients and methods: 44 patients were recruited from the Rheumatology outpatient clinic of the Kasr El-Aini Hospital, their mean age was 33 ± 8.7 years. Twenty age and sex matched subjects were included as controls. Dual energy X-ray absorptiometry (DEXA) was performed for the patients and control. Disease activity and physical function were assessed using the Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI), respectively.

Results: The *T*-scores of the spine, hip and forearm were lower in patients compared to controls. Low BMD was more found among patients with chronic sacroiliitis. There were significant negative correlations between chin to chest and occiput to wall distance and BMD at the hip and forearm (both $p < 0.05$). The BMD at the spine showed a significant correlation with the BASDAI ($p = 0.008$) and BASFI ($p = 0.03$). There was no correlation between BMD at any site and patients' age, disease duration, inflammatory back pain duration, modified Schöber's test, finger-to-floor test and laboratory parameters.

Conclusion: The BMD was remarkably decreased at all measurement sites in AS patients. The BMD at the spine significantly negatively correlated with the disease activity and physical function. Bone loss in AS can be explained partly by the role of inflammatory mediators and partly as a consequence of reduced physical activity.

* Corresponding author. Address: Faculty of Medicine, Cairo University, Manawat/Giza, Egypt. Tel.: +20 238171015.
E-mail address: dr.safaa_sayed@yahoo.com (S. Sayed).

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1. Introduction

Ankylosing Spondylitis (AS) is a chronic inflammatory rheumatic disease, mainly affecting the sacroiliac joints, vertebrae and intervertebral discs, leading to syndesmophyte formation and impaired back mobility [1].

In AS two enhanced but opposite bone remodelling processes are taking place in close vicinity within the spine which are pathologic new bone formation in the cortical zone of the vertebrae, the zygapophyseal joints, and the ligamentous apparatus and excessive loss of trabecular bone in the centre of the vertebral body leads to osteoporosis [2]. An increased prevalence of osteoporosis and significantly lower bone mineral density (BMD) in AS patients compared with sex and age matched controls have been demonstrated [3,4]. Measurement of bone mass is useful in diagnosing osteoporosis commonly observed in the lumbar spine and the femoral neck but not in the appendicular skeleton. Osteoporosis is seen early in the disease whereas increased bone mass is observed later or due to syndesmophyte formation. Osteoporosis in AS is probably a multi-factorial condition. Contributing factors are spine immobility secondary to ankylosis, inflammatory cytokines which enhance bone resorption, prolonged use of nonsteroidal antiinflammatory drugs (NSAIDs) and a deficit in sex hormone secretion [3,5]. Furthermore, there is no alteration in calcium or phosphorus metabolism in AS [6]. The only evidence-based recommendation is that optimal control of disease activity in AS prevents bone loss. A beneficial effect of infliximab therapy on bone turnover markers and BMD in AS has been shown; bisphosphonates may be useful in managing osteoporosis in AS [7].

Several surveys have reported the prevalence of vertebral fractures in AS patients [3,8,9]. These studies indicate that vertebral fractures are a regular finding in patients with AS but their prevalence is highly variable. These differences are at least in part a reflection of differences in recruitment methods (e.g. consecutive patients, selected patients based on disease activity or occiput-to-wall distance, sex distribution, age and clinical versus systematic morphometric fractures) and the definition of vertebral fractures. A detailed description of vertebral fractures in AS appears to be derived from the study by Cooper and colleagues [10]. This retrospective population-based study on clinical fractures reported an increased odds ratio (OR) of 7.7 (95% confidence interval 4.3–12.6) for clinical vertebral fractures. The cumulative incidence of clinical vertebral fractures was higher in men (OR 10.7 versus 4.2 in women) and increased during the first 5 years of the disease, peaking at 17%, 20–30 years after diagnosis. Of interest, the cumulative incidence of nonvertebral fractures was similar to the control population. As this population study involved clinical vertebral fractures, it still remains unclear what is the exact prevalence and incidence of morphometric vertebral fractures in AS.

The aim of this work was to assess the bone mineral density (BMD) in Ankylosing Spondylitis (AS) patients and to investigate its relation with clinical and laboratory parameters, imaging of sacroiliac joints, disease activity and physical function.

2. Patients and methods

In this cross-sectional study, 44 Ankylosing Spondylitis (AS) patients were recruited from the Rheumatology outpatients clinic Kasr El Aini Hospital, Faculty of Medicine, Cairo University. Patients were diagnosed according to the modified New York criteria [11]. Patients 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 spondyloarthropathies were excluded. The control group consisted of 20 age- and sex-matched healthy subjects without a history of inflammatory rheumatic disease, conditions or medication responsible for bone loss. The study was approved by the local ethics committee and was performed in accordance with ethical standards of the 1964 Declaration of Helsinki. Patients gave informed consent to be included in the study.

Demographic and clinical variables were recorded from all patients including age, disease duration, age of disease onset, peripheral arthritis, axial joints involved and uveitis.

Functional status and measures of disease activity and severity were obtained using established methods. Functional ability was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI) [12]. BASFI is a set of 10 questions designed to determine the degree of functional limitation in AS. It is a self-assessment tool where a 100 mm horizontal visual analogue scale (VAS) is used to answer the questions that reflect the ability to perform specific tasks. The mean of the ten scales gives the BASFI score, value between 0 and 100.

Disease activity was measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [13]. The BASDAI is also a self-assessment tool that evaluates a range of symptoms. Like the BASFI, the BASDAI consists of 100 mm horizontal VAS used to answer 6 questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, pain and swelling in other joints, discomfort with peripheral entheses and severity and duration of morning stiffness. To give each symptom equal weighting, the mean of two scores relating to morning stiffness is taken. The resulting score is then divided by 5 to give the final BASDAI score (0–100).

Spine mobility was assessed using the modified Schöber's test [14]. We have also recorded the patients' medication history including intermittent or continuous use of NSAIDs, disease-modifying drugs (DMARDs) and tumour necrosis factor-alpha (TNFα) blockers (Infliximab, Etanercept and Adalimumab). Sacroiliac and lumbosacral MRI were examined in order to grade the sacroiliitis that was defined by signal characteristic of the joint space, presence of bone marrow oedema or erosion adjacent to the joint (according to New York criteria) and to assess the syndesmophytes [15]. Chronic sacroiliitis was defined by low signal intensity on T1 and T2 weighted images, subchondral sclerosis, joint space narrowing and bone bridging. While, the presence of erosions as high signal intensity on T2 image, subchondral oedema and enhancement within or adjacent to the sacroiliac joint were considered markers of active inflammatory lesion. Inflammatory activity was also measured by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (by ELISA, normal values < 5 mg/L).

Bone mineral density (BMD) was measured at the postero-anterior (PA) lumbar spine (L2–L4), forearm and hip by means of dual energy X-ray absorptiometry (DEXA). Results were expressed as *T*-score (standard deviation from peak adult 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 [16].

Statistical analysis: The statistical program SPSS version 15 was used for statistical analysis. Results were expressed as mean (standard deviation), or number (percentage). 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 was performed when appropriate. The correlations between variables were presented as the Spearman's correlation coefficient (rho). A multivariate logistic regression analysis model was performed to detect any predictive risk factors for the low BMD. The level of statistical significance was <0.05 (2-tailed).

3. Results

Our study included 44 patients (42 males and 2 females), their demographic, clinical, and laboratory characteristics of the patient group are listed in Tables 1 and 2. Ninety-seven percent of the patients were receiving intermittent or continuous treatment with NSAIDs and 80% of the patients were also treated with at least one disease-modifying drug (sulphasalazine, methotrexate and leflunomide). Demographic, clinical and radiographic data of the patients are shown in Table 1.

All AS patients (100%) had inflammatory back pain, 20 (45%) had peripheral arthritis, 4 (9%) had unilateral and/or bilateral uveitis and 36 (82%) were HLA-B27 positive. None of the patients had syndesmophytes The BMI was comparable between patients and controls ($p = 0.4$) and there were no gender differences of value. The laboratory and osteodensiometric variables in patients and controls are shown in Table 2.

The *T*-scores of the spine, hip and forearm were lower in AS patients compared to controls. Significantly more AS patients were osteopenic at the hip ($p = 0.001$), at the lumbar spine ($p = 0.007$), and the forearm ($p = 0.008$) (Table 2). According to the WHO classification for osteoporosis for the lumbar spine, 8 (19%) AS patients were osteoporotic, 22 (50%) were osteopenic and 14 (31%) were normal (controls; 0%, 10%, 90% respectively). At the hip, 32 (73%) AS patients were osteopenic, 12 (27%) were normal and none of them was osteoporotic (controls; 20%, 80% respectively). While, at the forearm, 6 (14%) AS patients were osteopenic, 4 were osteoporotic and 34 (77%) normal (controls; 10%, 90% respectively) (Table 3).

Low BMD was more found among the patients with chronic sacroiliitis. Out of 30 patients with chronic sacroiliitis, 16 were osteopenic at the lumbar spine and 6 were osteoporotic. While, from 8 patients with acute sacroiliitis; 4 were osteopenic and 2 were osteoporotic. Significant association was found between the chronic sacroiliitis and osteopenia in the hip and lumbar spine (contingency coefficient, 0.72, $p = 0.001$, 0.75, $p = 0.001$ respectively). The classification of patients was done according to their MRI findings at the Sacroiliac joints and DEXA values at the lumbar spine (Table 4).

There were significant negative correlations between chin to chest & occiput to wall distance and BMD at the hip & forearm (both $p < 0.05$). The BMD at the spine showed a significant negative correlation with each of BASDAI ($p = 0.008$) & BASFAI ($p = 0.03$). There was no correlation between BMD at any site and patient's age, disease duration, inflammatory back pain duration, modified Schöber test, finger-to-floor test and laboratory parameters (ESR, CRP) ($p > 0.05$). (Table 5).

Table 1 Clinical and radiographic features of the Ankylosing spondylitis (AS) patients ($n = 44$).

Variables	AS patients ($n = 44$)	
	Range	Mean ± SD
Age (years)	19–57	32.97 ± 8.7
Age of onset (years)	18–42	29.60 ± 6.7
Disease duration (years)	1–27	5.6 ± 7.5
MS duration (minutes)	30–180	100.9 ± 50.9
IBP duration (years)	1–27	5.7 ± 7.5
Modified Scöber test (cm)	3–6.7	4.5 ± 0.8
Finger-to-floor test (cm)	25.5–56	40.1 ± 8.9
Chin-to-chest (cm)	0–0.5	0.05 ± 0.13
Occiput-to-wall (cm)	0–1	0.21 ± 0.33
Chest expansion (cm)	2–6	4.30 ± 1.05
BASDAI	1.8–8.8	5.70 ± 1.79
BASFAI	2.4–8	5.80 ± 1.42
MRI of sacroiliac: *n* (%)		
Normal	6	(13.6)
Acute sacroiliitis	8	(18.2)
Chronic sacroiliitis	30	(68.2)

AS: ankylosing spondylitis, MS: morning stiffness, IBP: inflammatory back pain, BASDAI: bath ankylosing spondylitis disease activity index, BASFI: bath ankylosing spondylitis functional index, MRI: magnetic resonance imaging.

Table 2 The laboratory and osteodensiometric features in AS patients and controls.

Variables	AS patients ($n = 44$)	Controls ($n = 20$)	*p* value
DEXA (*T* score)			
Spine	−1.12 ± 1.5	−0.41 ± 0.57	0.007
Hip	−1.27 ± 0.95	−0.46 ± 0.65	0.001
Forearm	−0.67 ± 0.93	−0.06 ± 0.69	0.008
ESR (mm/1st h)	42.68 ± 29.78	13 ± 8.1	0.001
CRP (mg/dl)	50.30 ± 57.66	4.8 ± 4.1	0.001

DEXA: dual energy X-ray absorptiometry, ESR: erythrocyte sedimentation rate, CRP: C reactive proteins.

Significant parameters in univariate analysis were tested in multivariate logistic regression model and showed no significant association between low BMD and each of the following; inflammatory parameters in MRI of the sacroiliac joint (OR: 0.01, $p = 0.9$), BASDAI (OR: 0.9, $P = 0.8$), BASFI (OR: 0.8, $P = 0.4$).

4. Discussion

The results of this cross-sectional study exploring the BMD at different measurement sites (spine, hip & forearm) 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 BMD at the spine was correlated with disease activity and function variables (e.g. BASDAI & BASFI) that reflected the cumulative damage of AS. In contrast, no correlation was found between BMD at any site and patient's age or disease duration.

Table 3 Bone mineral density in AS patients according to the WHO classification.

Site *N* (%)	DEXA		
	Normal	Osteopenic	Osteoporotic
Spine	14 (31)	22 (50)	8 (18)
Hip	12 (27)	32 (73)	0 (0)
Forearm	34 (77)	6 (14)	4 (9)

DEXA: dual energy X-ray absorptiometry.

Table 4 Spine DEXA in AS patients according to the MRI findings at the sacroiliac joint.

MRI	Lumbar spine DEXA	
	Osteopenic	Osteoporotic
Acute sacroiliitis	4	2
Chronic sacroiliitis	16	6

MRI: magnetic resonance imaging, DEXA: dual energy X-ray absorptiometry.

Table 5 Pearson correlation coefficients for BMD value versus other parameters.

Variables	Lumbar spine BMD	Hip BMD	Forearm BMD
*Age	0.95	0.14	0.41
*Dis. duration	0.92	0.64	0.26
*MS duration	0.45	0.76	0.78
*IBP duration	0.93	0.64	0.26
*Schober test	0.85	0.19	0.45
*Finger to floor test	0.26	0.93	0.54
*Occiput to wall	0.82	0.007*	0.001*
*Chin to chest	0.07	0.01*	0.001*
*BASDAI	0.008*	0.06	0.01*
*BASFAI	0.03*	0.77	0.67
*ESR	0.55	0.87	0.24
*CRP	0.29	0.7	0.21

BMD: bone mineral density, BASDAI: bath ankylosing spondylitis disease activity index, BASFAI: bath ankylosing spondylitis functional index, ESR: erythrocyte sedimentation rate, CRP: C reactive proteins.

* Statistically significant correlation ($p < 0.05$).

Our results agreed with previous studies that demonstrated lower BMD in AS patients [3,17,18]. 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 [3,10]. 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 all of the patients did not have syndesmophytes. In another study on a cohort of 103 patients with AS, Karberg et al. [19] 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 osteoporosis in AS, even in patients without syndesmophytes. In contrast to their finding, we did not find a significant relation between the BMD any site and disease duration.

The WHO criteria for the Osteoporosis 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 [16]. In our study, we found an increased prevalence of osteoporosis at the lumbar spine (18%) and osteopenia in 50% of the patients. These results were consistent with the reported prevalence of osteoporosis in AS varying from 18.7% to 62% [20]. We could not report the sex difference in our patients because most of them were males (42 males and only 2 females). The present study demonstrated a consistent, statistically significant BMD decrease at all measurement sites in patients with AS, as compared to age-matched healthy controls. In contrast, Franck et al. [21], examining 190 males with AS, had demonstrated a significant BMD reduction only in the hip.

Also we found that BMD at the spine was correlated with parameters reflecting the disease activity and function (BASDAI, BASFI); and the BMD at the hip correlated with parameters reflecting the cumulative damage of AS (occiput-to-wall and chin-to-chest tests). In contrast to the study of Muntean et al. [22], who found a significant correlation between the BMD at any site and disease activity parameters, while they found significant correlation between the BMD at the hip and the Schöber's test. The results suggested that bone loss in AS may involve different mechanisms at different stages of the disease.

By the Multivariate logistic regression analysis, we could not specify certain risk factor associated with low BMD in AS patients. On the other hand, Briot et al. [23,24], reported that the main risk factor associated with low BMD in AS patients was the presence of bone marrow oedema (inflammatory lesions) on MRI. The difference could be explained by the predominance of chronic sacroiliitis among our patients.

In conclusion, the BMD was remarkably decreased at all measurement sites in AS patients. The BMD at the spine significantly negatively correlated with the disease activity and physical function. Bone loss in AS, can be explained partly by the role of inflammatory mediators and partly as a consequence of the reduced physical activity. Larger scale longitudinal studies are recommended in future work to confirm our findings and to take into consideration the reduced bone density when treating AS patients.

Conflict of interest

No conflict of interest is declared by the authors.

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