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ORIGINAL PAPERS: CLINICAL OR BASIC RESEARCH

Bone mineral density in patients with ankylosing spondylitis

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ABSTRACT

Objective: *To determine bone mineral density (BMD) and the frequency of osteoporosis (OP) and osteopenia in ankylosing spondylitis (AS). A second objective was to investigate the relationship between BMD and clinical parameters.*

Methods: *Twenty-nine patients (23 male, 6 pre-menopausal female) were compared with 29 sex- and age-matched controls. BMD was evaluated at the lumbar spine and femoral neck by dual energy X-ray absorbtiometry (DEXA) using a DPX-alpha (Lunar-General Electric).*

Results: *In AS patients BMD was significantly reduced in both lumbar spine 1.08 ± 0.22 g/cm² (T = -1.23 ± 1.80) and femoral neck 0.88 ± 0.15 g/cm² (T= -1.30 ± 1.31) as compared with controls (1.16 ± 0.11 g/cm² [T= – 0.49 ± 0.80], respectively 0.96 ± 0.13 g/cm² [T= – 0.65 ± 1.04]) (all p < 0.05). According to the WHO definition, spine and hip OP was diagnosed in 34.48% and 20.68% AS patients respectively, with an additional 20.68% and 41.37% having osteopenia. We found no correlation between BMD and disease duration. Only spine BMD correlated with disease activity, as evaluated by erythrocyte sedimentation rate and serum C-reactive protein levels (r = – 0. 55, respectively – 0.48; both p < 0.01). In the subgroup analysis according to the presence or absence of syndesmophytes, the patients were grouped in advanced and mild AS categories, respectively. The mean BMD at the lumbar spine and femoral neck of patients with mild and advanced AS was similar (all p > 0.05). In the advanced AS patients, osteopenia and OP frequency was higher than in the mild AS patients, but the difference was not statistically significant (p > 0.05).*

Conclusions: *These results confirm that the majority of AS patients have decreased BMD values at both the lumbar spine and femoral neck. OP can be observed in early stages of the disease. The similar frequency of OP in mild and advanced AS suggests that immobility does not have an important role in pathogenesis. Patients with active disease are especially at risk for developing OP.*

Key words: ankylosing spondylitis, osteoporosis, bone mineral density

INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease characterized by spine and sacroiliac joint involvement that mainly affects young male subjects. Its clinical spectrum varies from a simple pelvic involvement (sacroiliitis) to a severe multisystemic and progressive disease (1). Syndesmophytes, which are due to new bone formation, are considered to be a hallmark of the disease. In parallel with this process, a reduction in bone formation also occurs. The presence of osteoporosis (OP) in AS patients has been confirmed by numerous researchers. For several years it has been established that bone mineral density (BMD) loss occurs early in the AS disease course. However, the pathogenesis of OP remains controversial. (2). The clinical significance in OP lies in development of fractures. Osteoporotic vertebral fractures are relatively common, but frequently unrecognized complications of AS, that can contributes to spinal pain and deformity of AS patients. Fractures frequently occurred as a result of minimal trauma and were associated with severe neurological deficits in a high proportion of patients (3, 4).

The aims of this study were to determine bone mineral density (BMD) and the frequency of OP and osteopenia in AS and whether BMD is correlated to duration and disease activity. ❑

PATIENTS AND METHODS

A total of 29 patients, 23 males and 6 pre-menopausal female, consecutively seen in our department were enrolled. All the patients fulfilled the modified New York criteria for primary AS (5). Patients excluded from this study were postmenopausal women, and those with other conditions that might alter bone metabolism (hyperthyroidism, hypogonadism, hyperparathyroidism, Paget's disease, liver and kidney disease, alcoholism, ongoing corticosteroid therapy, thyroxin, anti-convulsants and previous or current anti-osteoporotic treatment). All the patients were taken anti-inflammatory drugs (NSAIDs) and/or sulphasalazine. Clinical assessment of AS patients included demographic data: age, sex, weight, height, body mass index and disease duration. The presence of peripheral involvement, extra-articular manifestation (uveitis), and Schober's test measurement were also recorded. Laboratory activity was assessed by the Westergren's erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels. Patients were analyzed for sacroiliac joint changes (sacroiliitis, grades according to the New York scale [5]) and for the presence of syndesmophytes on postero-anterior and lateral dorsal and lumbar spine standard X-rays. All the patients were grouped according to the presence or absence of syndesmophytes, in advanced and mild AS categories, respectively.

The control group corresponded to 22 males and 7 pre-menopausal women without a history of inflammatory rheumatic disease or another condition which might alter bone metabolism.

BMD was evaluated at the L2-L4 lumbar spine (postero-anterior projection) and the left femoral neck by dual energy X-ray absorbtiometry (DEXA) using a DPX-alpha (Lunar Corporatin, USA). DEXA results were expressed as BMD (g/cm^2), as well as calculated T-score (number of standard deviations from the mean BMD of young healthy women) According to the World Health Organization (WHO), osteopenia was defined as a T score between -1 and -2.5 S.D. and osteoporosis as a T score below -2.5 S.D (6).

Statistical analysis

The results were analysed using the Statistical Package for Social Science (SPSS). The differences between the groups were tested for significance using the Student's *t*–test for unpaired data. Comparation of the frequency was done with Fischer's exact test. Pearson's correlation coefficient was used to study the correlation between BMD and the variables. *P* values< 0.05 were considered statistically significant. ❑

RESULTS

The clinical, biological and radiologic characteristics of AS patients are described in table 1. The demographic variables were similar between patients and controls (all $p > 0.05$; table 2).

In AS patients the mean BMD and the corresponding T scores were significantly reduced in both lumbar spine and femoral neck as compared with controls (all $p < 0.05$; table 3). Vetebral fractures were observed in 2 out of 29 patients (6.89%).

According to the WHO definition of OP we found that 34.48% of patients had OP, 20.68% had osteopenia and 44.84% had normal values at lumbar spine (controls: OP in 0%, osteopenia in 24.13% and normal values in 75.87%; $p = 0.03$). At the femoral neck we found OP in 20.68% of the patients, osteopenia in 41.37% and normal values in 37.93%, but the difference with the control group was not statistically significant (controls: OP in 3.44 %, osteopenia in 37.93% and normal values in 58.62%; $p = 0.18$).

We found no statistically significant correlation between BMD measured at any site and disease duration ($p > 0.05$). Only spine BMD correlated with disease activity, as evaluated by ESR and CRP levels ($r = -0.55$, respectively -0.48; all $p < 0.01$).

According to the presence or absence of syndesmophytes, the patients were grouped in advanced and mild AS categories, respectively. Patients with advanced AS (n=16) were significantly older (mean age 45.4 *vs* 34.7 years, $p = 0.002$), and had significantly longer disease duration (18.7 *vs* 6.4, $p = 0,001$) than those with mild AS. As expected, patients with advanced AS had reduced spinal mobility (evaluated by Schober's test) as compared with mild AS (advanced *vs* mild AS: 1.03 ± 0.8 *vs* 1.77 ± 1.17 cm; $p = 0.05$). In mild AS group 5 out of 13 patients (38.46%) were females, while in the

advanced AS group there was only 1 female, the majority of patients (93.75%) being males. Other demographic and clinical variables (age, weight, height, BMI, ESR and CRP levels, peripheral and extraarticular manifestations) were similar between advanced and mild AS patients (all $p > 0.05$). Lumbar spine BMD and the corresponding T score was significantly lower in male patients as compared with female patients (males *vs* females: 1.02 ± 0.21 g/cm^2 [T= -1.76 ± 1.58] *vs* 1.30 ± 0.10 g/cm^2 [T= 0.80 ± 0.88]; $p < 0.005$). The femoral neck BMD of male and female patients was similar ($p > 0.05$). In advanced AS patients lumbar spine BMD and the corresponding T score were increased as compared with mild AS patients, but the difference was not statistically significant ($p > 0.05$). The femoral neck BMD of patients with mild and advanced AS was similar ($p > 0.05$; table 4).

The osteopenia or OP frequency was found to be 69.22% at the lumbar spine and 76.91% at the femoral neck in the mild AS patients according to the T score defined by WHO. In the advanced AS patients, osteopenia and OP frequency was higher than in the mild AS patients (75% at the lumbar spine and 81.25% at the femoral neck), but the difference was not statistically significant ($p > 0.05$). ❑

	Mean	SD	Range
Age(yr)	40.6	10.1	21-60
Sex	23 male, 6 female		
Disease duration (yr)	13.21	9.45	1-32
Schober test (cm)	1.36	1.03	0-3
Sacroiliitis	Grade 2: 7 (24.13%) Grade 3 or 4: 22 (75.87%)		
Dorsolumbar syndesmophytes	16/29 (55.17%)		
ESR (mm/h)	31.45	27.58	3-124
CRP (mg/dl)	2.10	3.11	0-12.5
Peripheral disease	22/29 (75.86%)		
Extraarticular manifestations (uveitis)	3/29 (10.34%)		

TABLE 1. Clinical, biological and radiological characteristics of ankylosing spondylitis patients

	AS (n=29)	Controls (n=29)	*P*
Age (yr)	40.6 ± 10.1	41.6 ± 11.1	NS[a]
Sex (male/female)	23/6	22/7	NS[b]
Weight (kg)	69.0 ± 10.8	73.9 ±13.6	NS[a]
Height (cm)	171 ± 7.46	174 ± 7.03	NS[a]
BMI (kg/m^2)	23.7 ± 4.5	24.4 ± 3.8	NS[a]

TABLE 2. Comparative demographic data of ankylosing spondylitis (AS) patients and controls

[a]Student's *t*-test; [b]Fischer's exact test

	AS (n=29)	Controls (n=29)	*P*[a]
Lumbar spine BMD (g/cm^2)	1.08 ± 0.22	1.16 ± 0.11	0.03
T score	-1.23 ± 1.80	-0.49 ± 0.80	0.04
Femoral neck BMD (g/cm^2)	0.88 ± 0.15	0.96 ± 0.13	0.01
T score	-1.30 ± 1.31	- 0.65 ± 1.04	0.01

TABLE 3. Bone mineral density (BMD) measurements in ankylosing spondylitis (AS) patients and controls

[a]Student's *t*-test

	Mild AS (n=13)	Advanced AS (n=16)	*P*[a]
Lumbar spine BMD (g/cm^2)	1.04 ± 0.24	1.11 ± 0.21	NS[a]
T score	-1.35 ± 1.85	-1.03 ± 1.80	NS[a]
Femoral neck BMD (g/cm^2)	0.90 ± 0.16	0.89 ± 0.13	NS[a]
T score	-1.18 ± 1.58	- 1.46 ± 1.13	NS[a]

TABLE 4. Bone mineral density (BMD) measurements in mild and advanced ankylosing spondylitis (AS) patients

[a]Student's *t*-test

DISCUSSION

This study showed a reduction of BMD in the lumbar spine as well as the femoral neck in patients with AS. In the current literature there are several studies that examined bone mass in AS. Taken together, the results were similar, showing that BMD is reduced in AS patients in comparison with controls, with some differences according to the stage of the disease. Mulaji *et al*, found that patients with advanced AS had a significantly increased BMD of the lumbar spine both in comparison with the control group and with patients suffering mild disease (7). Donelly *et al*. found that patients with AS had significantly lower femoral neck BMD in proportion to disease severity and

duration. They also found that lumbar spine BMD was reduced in early disease, but in patients with advanced AS it has increased considerably (8). Devogelaer *et al.* reported a significant decrease in the lumbar spine BMD in mild AS, but in advanced AS the spine BMD values were similar to the normal controls (9). Although mild and advanced disease were defined according to various criteria, it seems likely that in advanced AS exists a false increase of BMD values, due to syndesmophyte formation and/or facet joint ankylosis (7, 8, 9, 10, 11). That's why, the anteroposterior lumbar DEXA results can be misleading when evaluating the extent of OP in late stage AS (11). In a recent study on a cohort of 103 patients with AS, Karberg *et al* reported that bone loss is more frequently detected in AS patients with syndesmophytes. They concluded that the method of bone density measurement is critical and should be different depending on disease duration. It was found that DEXA at the femoral neck is the most sensitive method for evaluating OP in AS, even in patients without syndesmophytes (12). The presence of syndemophytes had no distorting effect on BMD measured by lateral DEXA or on quantitative computerized tomography (QCT), these methods being more useful than anteroposterior lumbar DEXA in late stage AS patients (12,13,14). In our study, lumbar spine BMD values of the advanced cases were increased compared with the mild cases, but without statistical significance. Considering the low sensibility of anteroposterior DEXA in late stage cases, it's likely for these patients to have lower BMD values and more severe OP than actually measured.

The WHO criteria for the diagnosis of OP are based on BMD measurements of healthy white women, while AS is a disease that mainly affects male subjects. That's why it's necessary a control population when evaluating BMD in such a disease population. Despite this limitation, we applied these criteria and we found that more than a half of our patients have lumbar spine and femoral neck osteopenia and/or OP. In medical literature there have been reported different frequencies of osteopenia or OP in AS, ranged from 26% to more than 90 % (9, 11, 15, 16). The variations in the frequency might in part be explained by different characteristics of the study populations and by differences in methods of measurements.

In this study we found no correlation between BMD measured at any site and disease duration. However, there is some controversy regarding the relationship between BMD and disease duration. In a study realized by Capaci *et al*., they found a significant positive correlation between disease duration and lumbar spine BMD and a significant negative correlation between the disease duration and total hip BMD (11). Toussirot *et al*., on a cohort of 71 patients with early disease showed that only femoral neck correlated with disease duration (15). However, other researchers found no correlation between BMD and disease duration, suggesting that the chronicity of the disease is probably not involved in this bone loss (17, 18).

Bone loss in AS appears to be multifactorial and perhaps involves different mechanisms at different stages of disease (19). OP might be due to physical impairment, treatments, hormonal causes or systemic inflammatory activity.

Spinal changes in AS patients can reduce mobility, and it was suggested that immobility might be an etiologic factor. However, bone loss was observed in patients with early disease with similar or even greater levels of exercise compared with controls (20). In our study we found a similar frequency of osteoporosis in mild and advanced AS suggesting that immobility has not an important role in pathogenesis.

Treatments may in part play a role in pathophysiology of bone impairment in AS. Corticosteroids are rarely used in AS and NSAIDs have not been proved to cause OP in humans (2).

Some authors postulated a hormonal cause of OP in AS, showing that bone loss was correlated with low levels of sexual hormones (9, 21). In our study spine BMD was lower in men than in women. Similar results were obtained by some authors (8), while others could not find a difference between men and women (7, 11).

The most likely explanation for OP in AS is disease activity. In our study, we found a correlation between indices of disease activity (ESR and CRP levels) and spine BMD. In a recent study, biological markers of disease activity were higher in the subgroup of patients with low lumbar spine BMD than in the subgroup with normal values (22). In longitudinal studies it has been shown that bone loss occurred only in patients with persistent active disease (23, 24). Other researchers did not find any relationships between BMD measurements and disease activity

(15, 25). Bone turnover as evaluated by markers of collagen breakdown correlated negatively with disease activity and inflammatory parameters (16, 21, 26). Conversely, the biochemical markers of bone resorption did not correlate with BMD measurements at any site and this could be explained by the fact that BMD is a longitudinal variable while markers of turnover reflect the situation at a given point (2, 23, 26). It has been hypothesized that inflammatory cytokines [(tumour necrosis factor-α (TNF α), interleukin-6 (IL-6), IL-1] may play a role in the inflammatory process of AS and they are probably involved in this bone loss (16, 23). RANK-RANK ligand system and its natural inhibitor osteoprotegerin (OPG) is considered the key element in bone cytokine interrelation. Franck *et al*, found that OPG serum levels were significantly lower in patients with AS compared to controls and in contrast to controls, were not positively correlated with age, suggesting a lack of this resorption antagonist in AS (21). All of this data suggest that inflammatory mediators play a major role in the occurrence of OP in AS.

CONCLUSION

1. Majority of AS patients have decreased BMD values at both the lumbar spine and femoral neck.
2. OP can be observed in early stages of the disease.
3. The similar frequency of OP in mild and advanced AS suggests that immobility has not an important role in pathogenesis.
4. AS patients with laboratory evidence of active disease could have a higher risk of bone loss.

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