

Risk Factors of Bone Loss in Spondyloarthritis

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Abstract- We aimed to determine the bone mineral status in patients with spondyloarthritis (SA), and to assess the impact of parameters associated with bone loss on bone mineral density (BMD). Seventy-five patients (62 men) with SA fulfilling the modified New York criteria were included in a cross-sectional study during one year. BMD was assessed in all patients using dual-energy X-ray absorptiometry. The patient's average age was 36.8 years. Sixty-five patients (86.6%) had bone loss. The lumbar spine was the site most affected by osteoporosis (37%). Bone loss was significantly associated with low BMI, peripheral joint involvement, active disease (high ASDAS_{ESR} and BASDAI), vitamin D insufficiency, elevated erythrocyte sedimentation rate (ESR) and c-reactive protein, as well as high BASRI, high BASMI, and with the use of csDMARDs or anti-TNF alpha therapy. The disease activity, biologic inflammation, low vitamin D level, peripheral joint involvement, and structural damage were the major factors that induce bone loss in SA patients. Multivariate analysis showed that only high ESR level (AOR 19.9, 95% CI) and peripheral arthritis (AOR 14.5, 95% IC) were independent risk factors of bone loss. Our study shows that bone loss was a multifactorial complication of SA.

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Introduction

Spondyloarthritis (SA) is a chronic inflammatory disease affecting the spine and the sacroiliac joints, mainly in young males (1,2). While syndesmophyte formation and bone erosions at enthesitis sites have long been seen as hallmarks of skeletal involvement in SA, loss of bone mineral density (BMD) and disruption of bone remodeling were commonly overlooked. The reported prevalence of BMD loss among SA patients varied between 11.7% and 34.4% according to different sources in the literature and was common even during the first decade of the disease (3-5). Thus, patients with SA are at high risk of developing osteoporosis (OP) and fragility fractures, limiting their quality of life (5,6).

Osteoporosis associated with SA is now well recognized, thanks to epidemiological data, advances in techniques for measuring BMD, and a better understanding of this complication.

Although low BMD related to inflammation is considered a major determinant of bone fragility, there is much uncertainty regarding other risk factors associated with BMD loss during SA, especially hormonal factors.

Therefore, the early identification and management of these factors could offer a treatment advantage.

As there are few studies assessing the relationship between disease activity indexes, spinal mobility tests, and BMD loss in SA patients, we conducted a single-center study to determine the bone mineral status and hormonal profile in patients with SA, to search for parameters associated with bone loss, and to assess the impact of these factors on BMD.

Materials and Methods

Study design

This cross-sectional study was conducted in the Rheumatology Department of the Kassab Institute of Mannouba in Tunisia over the course of 1 year. Seventy-five patients were enrolled during their hospitalization.

Inclusion criteria

All consecutive SA patients fulfilling the modified New York criteria were included, regardless of their treatment regimen.

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Exclusion criteria

Patients with kidney, liver, thyroid, parathyroid, or oncological disease, or other diseases that can affect calcium and bone metabolism, were not included. Also, patients with spondyloarthritis associated with inflammatory bowel disease and patients taking corticosteroids, antipsychotics, anticonvulsants, L-thyroxin, anticoagulants, hormonal replacement therapy, or bisphosphonates, or undergoing other treatments that can interfere with bone metabolism, were not included.

Data collection

All patients provided a complete medical history and underwent clinical examination. Clinical assessment included a collection of demographic and clinical data (age, gender, ethnic group, and co-existing diseases) and SA characteristics (age of onset of SA, duration of the disease, evaluation of axial and peripheral joint involvement, spinal mobility measurements, and lists of medications taken).

Disease activity was assessed clinically and radiologically using the following indices: Bath ankylosing spondylitis disease activity index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score, Bath Ankylosing Spondylitis Radiologic Index (BASRI), and modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Data on bone mineral status were collected, including risk factors for OP, biological and hormonal test results, and 25-hydroxyvitamin D (25OHvitD) levels.

The hormonal assessment performed involved measuring thyroid hormones (free T4 thyroxin and thyroid-stimulating hormone), parathyroid hormone, sex hormones (testosterone and gonadotrophic hormones, follicle-stimulating hormone, and luteinizing hormone), and cortisolemia.

Patients self-reported whether or not they led a sedentary lifestyle, which was defined as having engaged during the previous month in fewer than 3 periods per week of physical activity that lasted at least 30 minutes (7).

Dual-energy X-ray absorptiometry measurements

Densitometry examination of patients was performed at the Rheumatology Department of the Kassab Institute.

Lumbar spine BMD (anterior-posterior projection at L1 - L4 and lateral projection) and total hip BMD were assessed in all patients as measured by dual-energy X-

ray absorptiometry (DXA) using the Prodigy Lunar system from General Electric.

Quality control procedures were carried out in accordance with the manufacturer's recommendations. Instrument variation was determined by a daily calibration procedure using a phantom supplied by the manufacturer. The precision error was < 2.0% for each measured site at a standard speed based on repeated scans in a random sample of 30 subjects.

The results were expressed for each of the 3 measurement sites in terms of BMD (g/cm²) after comparing these densities to a Tunisian reference population for women, to an Italian reference population for men, and to data from the U.S. National Health and Nutrition Examination Survey for the lateral spine projection measurements (Tunisian population reference data were not available for men nor for the lateral spine projection measurements). World Health Organization definitions were used to label osteopenia (T-score -1 to -2.5) and OP (T-score ≤ -2.5) for menopausal women as well as for men, given the lack of consensual definition of OP in men. Patients were considered as having bone loss if the T-score at any site was < -1.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software version 11.5.

Descriptive statistics were presented as frequencies and means ± standard deviations as appropriate. Comparisons were performed using a Student t-test and analysis of variance for normally distributed variables. Comparisons of percentages on independent series were made by the Pearson chi-square test. In the case of the nonvalidity of this test, we used the Fisher exact bilateral test. The links between 2 quantitative variables were assessed using the Pearson correlation coefficient. To identify factors associated with bone loss, we calculated the odds ratio. In addition, we performed a multivariate logistic regression analysis using backward selection, in order to calculate adjusted odds ratios, measuring the proper role of each risk factor independently related to bone loss. The level of significance for all statistical tests was set at ≤ 0.05.

Results

Patient characteristics:

A total of 75 Caucasian patients were included in the study. There were 62 men (82.6%) and 13 women (17.3%), with a median age of 36.8 years ± 11.8 (17 - 74

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years). Six patients (8%) had a body mass index (BMI) less than 19 kg/m² and 9 patients (12%) were obese (BMI >30 kg/m²). Active smoking and chronic alcoholism were reported in 32 (42.7%) and 8 (10.7%) patients, respectively. Mean dietary calcium daily

uptake was estimated at 618.3±194.3 mg/day (according to the Fardellone questionnaire). Eight women were menopausal at the time of the study. The demographic characteristics of patients and OP risk factors are summarized in Table 1.

Table 1. Osteoporosis risk factors involved in bone loss in patients with spondyloarthritis

| Parameter | Value | BMD | | | T score | | | Bone loss |
|---|--------------|-------------------|-------------------|-------------------|--------------------|--------------------|-------------------|-----------|
| | | AP | LS | F | AP | LS | F | |
| Sex (Male) n (%) | 62 (82.7) | p=0.01 | p=0.16 | p=0.09 | p=0.94 | p=0.82 | p=0.45 | p=0.19 |
| Mean BMI (Kg/m ²) | 24.9 ± 4.5 | p=0.24 r=0.13 | p=0.92 r=0.01 | p=0.17 r=0.16 | p=0.38 r=0.10 | p=0.12 r=0.17 | p=0.28 r=0.12 | p=0.03 |
| Coffee consumption n (%) | 33 (42.7) | p=0.23 | p=0.38 | p=0.60 | p=0.93 | p=0.009 | p=0.22 | p=0.17 |
| Early menopause n (%) | 4 (50) | p=0.01 | p=0.01 | p=0.12 | p=0.15 | p=0.33 | p=0.85 | p=0.31 |
| Parity n (%) | 11 (84.6) | p=0.95 r=-0.01 | p=0.96 r=0.012 | p=0.67 r=-0.13 | p=0.006 r=-0.71 | p=0.30 r=-0.30 | p=0.23 r=-0.35 | p=0.30 |
| Sedentary lifestyle n (%) | 47 (62.6) | p=0.53 | p=0.15 | p=0.30 | p=0.73 | p=0.03 | p=0.2 | p=0.21 |
| Mean ESR (mm/hr) | 34.9 ± 23.8 | p=0.32 r=-0.11 | p=0.16 r=-0.16 | p=0.16 r=-0.16 | p=0.09 r=0.20 | p=0.003 r=-0.34 | p=0.23 r=-0.14 | p=0.001 |
| Mean CRP (mg/l) | 15.0 ± 17.49 | p=0.93 r=0.01 | p=0.48 r=0.08 | p=0.73 r=0.04 | p=0.23 r=-0.14 | p=0.03 r=-0.24 | p=0.01 r=-0.29 | p=0.01 |
| Mean 25 OH Vitamine D level (ng/ml) | 12.8 ± 6.48 | p=0.01 r=0.27 | p=0.08 r=0.19 | p=0.04 r=0.22 | p=0.12 r=0.18 | p=0.27 r=0.12 | p=0.07 r=0.20 | p=0.02 |
| Mean PTH level (pmol/ml) | 2.4 ± 1.4 | p=0.95 | p=0.49 | p=0.93 | p=0.87 | p=0.68 | p=0.18 | p=0.11 |
| Sex hormone disruption n (%) | 7 (9.3) | p=0.53 | p=0.80 | p=0.51 | p=0.94 | p=0.02 | p=0.27 | p=0.36 |

AP: anterior-posterior; BMD: bone mass density; BMI: body mass index; CRP: c reactive protein; ESR: erythrocyte sedimentation rate; F: femoral; LS: lateral spine; PTH: parathormone; bone loss defined as T score ≤ -1

Spondyloarthritis characteristics

The mean duration of the disease was 9±7.9 years. Exclusively axial involvement was observed in 36 SA patients (48%).

Twenty-seven patients (36%) received conventional synthetic disease-modifying antirheumatic drugs (csDMARDs): 24 patients were under sulphasalazine, and 3 patients were under methotrexate (MTX).

The clinical, therapeutic, and specific parameters of SA are summarized in Table 2.

Bone mineral status

The femoral site BMD was measured only in 69 patients because of 6 cases of total hip replacement. Sixty-five patients (86.6%) had bone loss (osteopenia in 31 cases; OP in 34). The lumbar spine (on lateral projection) was the site most affected by OP (26 cases, or 37%). The results of BMD measurement are summarized in Table 3.

Table 2. Association between specific disease parameters and BMD parameters in patients with Spondyloarthritis

| SA specific Parameters | Value | BMD | | | T score | | | Bone loss |
|---|--------------|--------------------|-------------------|-------------------|--------------------|--------------------|-------------------|-----------|
| | | AP | LS | F | AP | LS | F | |
| Age at the onset of the disease (years) | 27.8 ± 9.9 | p=0.62 r=-0.05 | p=0.16 r=-0.16 | p=0.86 r=0.02 | p=0.45 r=-0.08 | p=0.31 r=-1.18 | p=0.48 r=-0.08 | p=0.410 |
| Juvenile SA n (%) | 6 (8) | p=0.84 | p=0.86 | p=0.40 | p=0.77 | p=0.97 | p=0.98 | p=0.200 |
| Disease duration (years) | 9 ± 7.9 | p=0.97 r=-0.003 | p=0.15 r=0.16 | p=0.53 r=-0.07 | p=0.21 r=0.14 | p=0.59 r=-0.06 | p=0.34 r=-0.11 | p=0.410 |
| Peripheral arthritis n (%) | 39 (52) | p=0.91 | p=0.68 | p=0.78 | p=0.06 | p=0.20 | p=0.024 | p=0.002 |
| Hip arthritis n (%) | 37 (49.3) | p=0.71 | p=0.17 | p=0.79 | p=0.95 | p=0.01 | p=0.56 | p=0.330 |
| BASMI | 4.2 ± 2 | p=0.16 r=-0.16 | p=0.14 r=-0.16 | p=0.13 r=-0.17 | p=0.14 r=-0.17 | p=0.001 r=-0.36 | p=0.02 r=-0.25 | p=0.040 |
| BASFI | 3.8 ± 2.5 | p=0.58 r=-0.06 | p=0.21 r=-0.14 | p=0.67 r=-0.05 | p=0.75 r=-0.03 | p=0.03 r=-0.24 | p=0.13 r=-0.17 | p=0.070 |
| BASDAI | 3.5 ± 2.4 | p=0.54 r=-0.07 | p=0.33 r=-0.11 | p=0.51 r=-0.07 | p=0.65 r=-0.05 | p=0.19 r=-0.15 | p=0.18 r=-0.15 | p=0.040 |
| MASES | 1.6 ± 2.49 | p=0.07 r=-0.25 | p=0.89 r=-0.01 | p=0.10 r=-0.22 | p=0.22 r=-0.17 | p=0.63 r=-0.06 | p=0.42 r=-0.11 | p=0.340 |
| ASDAS _{ESR} | 3.1 ± 0.94 | p=0.32 r=-0.13 | p=0.20 r=-0.17 | p=0.38 r=-0.11 | p=0.95 r=-0.008 | p=0.03 r=-0.28 | p=0.12 r=-0.20 | p=0.009 |
| ASDAS _{CRP} | 3 ± 0.83 | p=0.74 r=-0.04 | p=0.59 r=-0.07 | p=0.2 r=0.001 | p=0.64 r=0.06 | p=0.12 r=-0.20 | p=0.01 r=-0.32 | p=0.070 |
| BASRI (sacroiliac joint) | 3.3 ± 0.8 | p=0.02 r=-0.27 | p=0.67 r=-0.05 | p=0.10 r=-0.20 | p=0.17 r=-0.16 | p=0.16 r=-0.17 | p=0.06 r=-0.22 | p=0.004 |
| BASRI (hips) | 1.6 ± 1.7 | p=0.63 r=-0.05 | p=0.08 r=-0.02 | p=0.28 r=-0.13 | p=0.11 r=-0.19 | p=0.004 r=-0.35 | p=0.02 r=-0.28 | p=0.005 |
| BASRI (spine) | 1.95 ± 1.55 | p=0.86 r=-0.01 | p=0.29 r=-0.12 | p=0.39 r=-0.1 | p=0.78 r=-0.03 | p=0.007 r=-0.30 | p=0.16 r=-0.16 | p=0.16 |
| BASRI (Total) | 8.9 ± 4.2 | p=0.56 r=-0.006 | p=0.34 r=-0.11 | p=0.29 r=-0.12 | p=0.42 r=-0.09 | p=0.001 r=-0.36 | p=0.06 r=-0.21 | p=0.04 |
| mSASSS | 17.6 ± 19.62 | p=0.42 r=0.10 | p=0.5 r=-0.08 | p=0.11 r=-0.20 | p=0.70 r=-0.04 | p=0.75 r=-0.04 | p=0.40 r=-0.11 | p=0.42 |
| Treatment (csDMARDs) n (%) | 27 (36) | p=0.47 | p=0.21 | p=0.51 | p=0.02 | p=0.75 | p=0.06 | p=0.04 |
| Physical treatment n (%) | 56 (86.6) | p=0.15 | p=0.80 | p=0.42 | p=0.95 | p=0.88 | p=0.87 | p=0.17 |

AP: anterior-posterior; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASRI: Bath Ankylosing spondylitis radiologic index; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; F: femoral; LS: lateral spine; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; mSASSS: modified Stoke ankylosing spondylitis spine score; SA: Spondyloarthritis; Bone loss defined as T score ≤ -1

Table 3. Patient distribution according to T score results

| Parameter | Mean BMD (g/cm ²) | Normal | | Osteopenia | | Osteoporosis | |
|-----------------|-------------------------------|--------|----|------------|----|--------------|----|
| | | n | % | n | % | n | % |
| Lumbar spine AP | 0.658 ± 0.24 | 25 | 35 | 26 | 37 | 20 | 28 |
| Lumbar spine LP | 0.633 ± 0.271 | 26 | 37 | 19 | 26 | 26 | 37 |
| Total hip | 0.933 ± 0.16 | 31 | 48 | 20 | 31 | 14 | 21 |

AP: anterior-posterior projection; LP: lateral projection; BMD: body mass density

Biological parameters and hormonal profile

Phosphocalcic and renal status were normal in all patients, as were thyroid hormone and cortisol levels. The 25OHvitD levels were low in 73 patients (97.3%), with vitamin D deficiency (level < 10 ng/ml) in 30 cases (41%) and vitamin D insufficiency (level between 10 and 30 ng/ml) in 43 cases (58.9%). Thirteen patients (17.3%) had a high parathormone level related to

vitamin D deficiency. Seven patients (5 men and 2 non-menopausal women) had sex hormone disruption suggesting hypogonadism with a low level of testosterone (in 5 men) and a high level of gonadotrophic hormones in all patients.

Assessment of parameters influencing bone mineral density in patients with spondyloarthritis

Bone loss in spondyloarthritis

Bone loss (T-score <-1 at the lumbar or femoral site) was significantly associated with low BMI, peripheral joint involvement in SA, active disease (high ASDAS_{ESR} and BASDAI), vitamin D insufficiency, elevated erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) level, high BASRI (sacroiliac, hips, and total), high BASMI, and the use of csDMARDs.

At the femoral site, a low T-score was significantly associated with peripheral-joint involvement in SA, high ASDAS_{CRP} score, high CRP level, high BASMI score, and high BASRI score (hips).

At the lumbar spine (anterior-posterior projection), low BMD was associated with female gender, early menopause, low vitamin D level, and high BASRI score at the sacroiliac. Moreover, the T-score at the lumbar spine (anterior-posterior projection) was associated with elevated parity and the use of csDMARDs.

When considering lateral projection at the lumbar spine, low BMD was associated only with early

menopause and vitamin D level, whereas the T-score was correlated to coffee consumption, sedentary lifestyle, coxitis, ASDAS_{ESR}, BASFI, ESR, CRP, inflammatory syndrome, sex hormones disruption, BASMI, and BASRI (hips, spine, and total).

Age, smoking, chronic alcoholism, and low calcium intake, all classical risk factors for OP, were not associated with bone loss at any of the measurement sites ($P = 0.45$, $P=0.31$, $P=0.09$, $P=1.3$, respectively).

Univariate analysis found that disease activity, biologic inflammation, low vitamin D level, peripheral joint involvement, and structural damage were the major factors associated with bone loss in patients with SA in this study.

Multivariate analysis showed that only high ESR level (AOR 19.9, 95% CI) and peripheral arthritis (AOR 14.5, 95% CI) were independent risk factors for bone loss (Table 4).

Table 4. Multivariate analysis of different risk factors for bone loss in patients with Spondyloarthritis

| Factor | Normal BMD | | Bone loss | | Crude OR (IC 95%) | P | Adjusted OR (IC 95%) | P |
|----------------------|----------------------|-----|-----------|-----|----------------------|----------------|-------------------------|--------|
| | N | (%) | N | (%) | | | | |
| SA Forms | Axial | 2 | 5.1 | 37 | 94.9 | 9.3 [1.9-45] | 14.5 [1.3-151.5] | 0.002 |
| | Axial and peripheral | 12 | 33.3 | 24 | 66.7 | | | |
| 25 OH Vit D | <20ng/ml | 9 | 13.8 | 56 | 86.2 | 6.2 [1.5-25.9] | 0 [0-0] | 0.016 |
| | >20ng/ml | 5 | 50 | 5 | 50 | | | |
| BASRI total | >= 10 | 2 | 65 | 29 | 93.5 | 6.4 [1.3-31.6] | 2.39 [0.183-31.3] | 0.013 |
| | < 10 | 11 | 30.6 | 25 | 69.4 | | | |
| ESR | High | 1 | 2.4 | 41 | 97.6 | 27.3 [3.3-226] | 19.9 [1.9-203.6] | <0.001 |
| | Normal | 12 | 40 | 18 | 60 | | | |
| ASDAS _{ESR} | =3.15 | 1 | 3.4 | 28 | 96.6 | 9.8 [1.1-86] | 1.52 [0.08-26.8] | 0.023 |
| | <3.15 | 7 | 25.9 | 20 | 74.1 | | | |

SA: Spondyloarthritis; BASRI: Bath Ankylosing spondylitis radiologic index; ESR: Erythrocyte sedimentation rate; ASDAS: Ankylosing Spondylitis Disease Activity Score

Discussion

Several studies have assessed OP and fracture risk in patients with SA (3-5). Nevertheless, to the best of our knowledge, this is one of the few studies evaluating the relationship between disease activity indices, spinal mobility tests, radiographic scores, laboratory findings, hormonal tests, and BMD loss in patients with SA.

The reported prevalence of bone loss among patients with SA varies between 11.7% and 34.4% (3). In our study, the frequency of OP varied from 21% to 37% according to the site of measurement (Table 3). Nevertheless, BMD decrease affected 81.3% of patients. Our results are similar to those in the Maghreb series, where the frequency of OP varied from 13.7% to 41.2% (8). However, our frequencies differ from those found in European (7.7% to 76.9% (9-11)) and Asian series (1%

to 42% (12)). The divergence of these results could be explained by the use of different measurement techniques, differences in sites studied, and the ethnic heterogeneity of the populations being compared.

Bone loss during SA had been noticed even before the advent of BMD measurement techniques. Indeed, several series have reported radiological bone rarefaction and/or vertebral collapse at the radiographic examination, as well as a high frequency of fragility fractures (13-16).

Interestingly, a number of studies have shown that many patients with vertebral fractures have a normal or only slightly diminished BMD as measured with DXA, suggesting that BMD could be overestimated by DXA in anterior-posterior projection (5,17). This issue could be overcome by using lateral lumbar spine projection, as in our study, which has the advantage of excluding the

posterior arch and reducing the impact of the bone construction process on BMD measures. Other tools, such as trabecular bone score (TBS), were developed to reflect bone microarchitecture and evaluate bone quality. Boussoualim *et al.*, (18) have evaluated TBS in a cohort of SA patients and showed that lumbar BMD was positively correlated with TBS ($r=0.61$), while disease duration, disease activity score, and serum parathormone levels were negatively correlated with TBS ($r=-0.24$, $r=-0.33$, and $r=-0.27$, respectively).

In addition, more than half of the patients with a BMD level above a -2.5 T-score had a low TBS value. Furthermore, Kang *et al.*, (19) reported that spinal radiographic progression and inflammatory markers were independently correlated with low TBS. Therefore, TBS could be a useful tool to identify the risk of OP and fragility fracture and, coupled with BMD, could provide additional information on the bone status of patients with SA (18,19).

In contrast with data found in the general population, the lifestyle factors of patients with SA in our study, including smoking, chronic alcoholism, and daily intake of calcium, did not seem to have an additional impact on BMD. However, in line with the findings of Hallström *et al.*, (20), we found that excessive coffee consumption reduced the lateral lumbar T-score significantly.

The frequency of hypovitaminosis D in patients with SA is still controversial. In fact, Durmus *et al.*, (21) did not find any difference between SA patients and same-age controls in 25OHvitD, serum calcium, phosphorus, or parathormone levels. However, Lange *et al.*, (22) demonstrated that high inflammatory activity of SA seems to lead to a decrease in serum levels of 25OHvitD and an increase in parathormone, with a negative impact on bone remodeling. Similarly, Malterre *et al.*, (23), in their series of 50 SA patients, demonstrated a depleted level of 25OHvitD in 70% of cases without osteomalacia stigmas or renal failure.

Few authors have investigated the hormonal profile and its impact on bone mass in patients with SA. Mitra *et al.*, (24) showed that sex hormones are not altered significantly in SA patients and do not appear to be related to BMD or vertebral fractures. However, Onose *et al.*, (25) reported that some of their SA patients had a certain degree of hypogonadism, as was found in our study that was asymptomatic but could lead to bone loss.

Functional limitation in patients with SA is related to both disease activity and structural damage, but the impact of these 2 factors on bone remodeling is not well known. Several authors have assessed the relationship between disease activity (evaluated by BASDAI and

ASDAS) and bone loss; most did not find any significant association (26-28). In our study, however, high BASDAI and ASDAS scores were significantly associated with bone loss, though multivariate analysis found that this association seems to be not independent. The discrepancy between these results highlights the subjective character of the BASDAI score. Otherwise, disease activity seems not to be a major factor in bone loss in SA.

Concerning structural damage, Ghazlani *et al.*, (29) showed a negative correlation between the BASRI score and femoral BMD. Similarly, Klingberg *et al.*, (30) found that the mSASSS score was higher in the subgroup of SA patients with lower BMD at the anterior-posterior and lateral lumbar sites as well as at the femoral neck site.

In our study, patients with bone loss had higher BASRI and mSASSS scores, confirming the negative impact of structural damage and spine ankylosing, which create relative immobilization in the patient leading to bone loss.

Thus, it can be concluded that the structural impact of SA is a confirmed risk factor for bone loss.

Several studies have found a significant correlation between biological inflammation and a decrease in bone mass (31-33). In accordance with these results, our study showed that elevated ESR and CRP levels were associated with lower T-score at lumbar and femoral sites. This association was also confirmed in multivariate analysis, where ESR level was demonstrated to be an independent factor in bone loss, multiplying the risk by 9.23. In fact, accelerated bone loss in patients with inflammatory disorders can be explained, in part, by the role of proinflammatory cytokines, generated by chronic inflammation, as regulators of bone resorption.

High-dose MTX has been linked with bone loss in oncology patients. Nevertheless, Cranney *et al.*, (34) suggested that low-dose MTX did not have a negative effect on bone density, at either cortical or trabecular sites. In contrast, Vosse *et al.*, (16) have demonstrated that the use of sulphasalazine was associated with fragility fractures in patients with SA.

In our series, 27 patients were receiving csDMARDs. We found that the T-score at the anterior-posterior lumbar spine was significantly lower in these patients, with a significant association with bone loss. Nevertheless, we have to note that patients taking csDMARDs in our study had peripheral arthritis, which could be a confounding bias, and, in this case, bone loss may not have been related to the effects of treatment but

to the severity of the SA.

The advent of anti-TNF α therapy has allowed both clinical and biological improvement of SA, but it also appears to have a significant positive effect on bone mass (35,36). In a recent study, Siu *et al.*, (37) reported that the use of anti-TNF α was associated with improved lumbar spine and hip BMD. This result may have been related mainly to the better control of inflammation (38).

The hallmark of our study was the multivariate analysis, which highlighted parameters independently related to the risk of bone loss. In fact, high ESR levels and the presence of peripheral arthritis were found to be independent risk factors for a bone loss regardless of other factors. This relationship may be related to decreased activity level when reaching the peripheral joints (especially weight-bearing activity) and may reflect the level of inflammation.

Thus, we can consider SA patients with high ESR levels and peripheral arthritis were more at risk of bone loss than other patients, suggesting the start or strengthening of treatment as soon as possible in order to prevent bone loss.

In summary, bone loss during SA is an early and direct complication related to the disease and correlated with its severity. Bone loss is caused by multiple factors, including disease activity, functional disability, treatment, and specific risk factors for OP. High ESR level and the presence of peripheral arthritis were found to be independent risk factors for a bone loss regardless of other factors.

The recognition of these risk factors is an important step in an OP prevention strategy for patients with SA, allowing healthcare providers to better target the population at risk of OP and to manage it early.

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