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Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort

Karine Briot,[1] Anne Durnez,[1,2] Simon Paternotte,[1] Corinne Miceli-Richard,[3] Maxime Dougados,[1] Christian Roux[1]

[1]Department of Rheumatology, Cochin Hospital, Paris Descartes University, Paris, France
[2]AZ Groeninge Hospital, Kortrijk, Belgium
[3]Department of Rhumatologie, Université Paris-Sud 11, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris (AP-HP), Le Kremlin Bicêtre, Paris, France

Correspondence to
Dr Karine Briot, Department of Rheumatology, Cochin Hospital, Paris Descartes University, Paris 75014, France;
karine.briot@cch.aphp.fr

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ABSTRACT

Objectives To assess bone mineral density (BMD) at lumbar spine and hip in a large cohort of patients with early inflammatory back pain (IBP) suggestive of axial spondyloarthritis (SpA), and to assess systemic and bone inflammation (according to MRI) as risk factors of low BMD.

Patients and Methods 332 (52.4% male) patients with IBP suggestive of axial SpA defined by Calin or Berlin criteria were recruited; they had lumbar spine and hip BMD and body composition measurements. Low BMD was defined by Z≤−2 (at least one site). Clinical, biological (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) and imaging (x-rays, spine and sacroiliac joint MRI) parameters were compared in patients with and without low BMD (Z≤−2). Significant parameters in univariate analysis were tested in multivariate models.

Results Patients (mean age 33.8 years) had a short duration of axial symptoms (mean 1.6 years); 71.4% fulfilled the Assessment of Spondyloarthritis International Society criteria for axial SpA and HLA-B27 was present in 62.1%. 43 (13.0%) had low BMD (88% male). Multivariate logistic regression showed that parameters significantly associated with low BMD (any site) were the presence of bone marrow oedema (inflammatory lesions) on MRI (OR 4.63, p=0.001), either ESR or CRP (OR 2.60, p=0.037) and male gender (OR 9.60, p=0.0004).

Conclusions This study conducted in a large cohort of young adults with early IBP suggestive of SpA shows that 13.0% of patients have a low BMD and that the main risk factor associated with low BMD was inflammation on MRI.

INTRODUCTION

Patients with ankylosing spondylitis (AS) have an increased risk of osteoporosis,[1–5] which can be observed in the early stages of the disease,[6 7] suggesting that it is not only related to spinal immobilisation as observed in advanced cases. The prevalence of osteoporosis according to bone mineral density (BMD) measurements is 14–27% and 4–14% at the spine and hip, respectively, which is unexpectedly high in these patients aged on average 30–40 years.[6–9] Bone loss in AS is observed in patients with sustained inflammation as assessed by serum parameters,[10 11] suggesting a systemic bone effect of inflammation. An increased risk of fracture has been reported in AS,[12] but only for vertebral fractures,[13 14] and there is no evidence of an increased risk of non-vertebral fractures, suggesting that factors other than systemic osteoporosis are determinants of this vertebral fragility.

Inflammatory back pain (IBP) is the hallmark of AS. Patients with early IBP may have an early axial involvement of AS, without typical structural changes. In such patients the bone inflammation (as assessed by MRI) may be responsible for an increased bone resorption and early decrease in bone density.

The French Society of Rheumatology initiated a large national multicentre cohort called Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) to facilitate investigations on diagnostic and prognostic markers but also aetiologicsl, pathogenic and socioeconomic factors among patients with early IBP suggestive of axial spondylarthropathies.[15]

The aims of this study were to assess BMD at the lumbar spine and hip in the patients from the DESIR cohort and to assess systemic and bone inflammation (according to MRI) as risk factors associated with low BMD.

PATIENTS AND METHODS

Study population: the DESIR cohort

This is a longitudinal prospective cohort studying subjects with IBP of recent onset and recruited from 25 regional centres in France.[15] Participants in the study gave their written informed consent. A detailed description of the centres, organisation of the cohort and full detailed protocol are available at the following address: http://www.lacohortedesir.fr.

The cohort included patients aged over 18 years and under 50 years with IBP as defined by Calin and/or Berlin criteria[16 17] for more than 3 months and less than 3 years and symptoms suggestive of spondyloarthritis (SpA) according to the local rheumatologist's assessment (eg, score≥5 on a numerical rating scale of 0–10, where 0 is not suggestive and 10 is very suggestive of SpA).

The exclusion criteria were: other spinal disease clearly defined (eg, discarthrosis); history of any biotherapy; history or current disorders that might interfere with the validity of the informed consent and/or prevent optimal compliance of the patient with the cohort. Corticosteroid intake was permitted only in doses of less than 10 mg prednisone per

day and had to be stable for at least 4 weeks before baseline.

A total of 708 patients with IBP was included between October 2007 and April 2010. Patients were evaluated every 6 months during the first 2 years and then on a yearly basis for an expected total follow-up duration of 10 years.

In the present study, we used the data collected at the first visit in centres performing BMD measurements and axial MRI in all their included patients (n=332).

Parameters collected

The following parameters were collected at the baseline visit.

Clinical parameters: duration of symptoms (defined as the time difference between the fist axial symptom and the initial interview), activity and severity parameters of the disease using questionnaires self-assessed by the patient: Bath ankylosing spondylitis global assessment (BAS-G) (0–100)); Bath ankylosing spondylitis disease activity index (BASDAI) (0–100); Bath ankylosing spondylitis functional index (BASFI) (0–100)); spinal mobility as measured by the Bath ankylosing spondylitis metrology index (BASMI) (0–10)) and the use of non-steroidal anti-inflammatory drugs (NSAID) were assessed. Patients were classified as having a diagnosis of axial SpA using the Assessment of Spondyloarthritis International Society (ASAS) criteria.[18]

Risk factors for osteoporosis: age, gender, menopause, tobacco use, alcohol excess, height, weight, body mass index (BMI) (kg/m^2), and the presence of inflammatory bowel disease were collected.

Biological parameters: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and presence of the HLA-B27 antigen were assessed. The ankylosing spondylitis disease activity score (ASDAS)–CRP was then calculated using CRP.[18] Abnormal CRP is defined by CRP above 6 mg/l.

Imaging modalities (x-rays and MRI evaluation): presence of sacroiliitis was determined on pelvic anteroposterior x-rays using a specific procedure. The investigator (local radiologist or rheumatologist) had to quote each sacroiliac joint as normal/doubtful/obvious/fusion and radiographic sacroiliitis was defined as the presence of obvious lesions of at least one sacroiliac joint. Lumbar spine radiographs were scored using the Stoke AS spine score.[19] T1-weighted fast spin echo and short τ inversion recovery 1–1.5 tesla MRI of the whole spine and the sacroiliac joints were performed to assess inflammatory and structural changes at baseline. The investigator (local radiologist or rheumatologist) gave binary information: presence of inflammatory lesions; as bone marrow oedema (BMO) (yes/no) at the spine (vertebral corner) and sacroiliac joints (subchondral oedema) according to the ASAS recommendations.[20]

BMD measurements

BMD was measured by dual-energy x-ray absorptiometry at baseline for all included patients in 12 centres (ie, half of the participating centres) with investigators having expertise in BMD measurements. The BMD measurements were carried out using Hologic, Inc. or Lunar (GE Healthcare) devices by experienced investigators. BMD was determined at the lumbar spine (second to fourth vertebrae) and the upper part of the left femur (total femur and femoral neck). The results were given as BMD (g/cm^2), Z and T scores. There is no consensus on the definition of low BMD in young adults. The International Society of Clinical Densitometry recommends using the threshold of −2 SD in Z score for the definition of low BMD; the WHO definition based on T scores cannot be applied in non-menopausal women and men below 50 years.[21] We checked for differences between these Z and T scores values. They were equivalent at the spine (–0.35 ±1.31, p=0.4) but there was a statistically significant difference at the hip (T=−0.17 (±1.10) vs Z=−0.08 (±1.07), p<0.0001). Therefore, we conducted our primary analysis using Z≤2 as a low BMD definition; then another analysis using the T≤−2 threshold for this definition. One site was defined by total lumbar spine (L1–L4), or total hip, or femoral neck. Z and T scores were determined according to references provided by the manufacturers. Gender-specific Z and T scores were based on female and male reference curves. Body composition (total lean and fat masses (kg), % fat mass) was measured using dual-energy x-ray absorptiometry from the whole body scan. All examinations were performed according to the manufacturer's recommendations. Devices were controlled by measuring a spine phantom at least theee times a week throughout the study; all examinations were performed according to the manufacturer's recommendations.

Statistical analysis

Data are expressed as mean (±SD). Differences in baseline characteristics between AS patients with low BMD and AS patients with normal BMD were evaluated using independent t tests for normally distributed variables, Mann–Whitney U tests for skewed variables and Pearson χ^2 tests for dichotomous variables. Univariate logistic regression analyses were performed to investigate associations between the presence of low BMD and disease-related factors (p<0.05 was considered statistically significant). Multivariate logistic regression analyses were performed by backward selection, removing variables that showed an association with the outcome measure with a p value above 0.20. The accuracy of the multivariate models was measured by the area under the curve (AUC). The database used in our study was locked on 30 June 2010 (intended follow-up of the cohort 10 years). All analyses will be performed by a statistician using SAS software, V.9.1.

RESULTS

Characteristics of the population

Three hundred and thirty two patients (52.4% male) were analysed in this study; their baseline characteristics were similar to those of the global DESIR population,[14] and are presented in tables 1 and 2. Two hundred and thirty seven (71.4%) fulfilled the ASAS criteria for axial AS.[18] HLA-B27 was positive in 62.1% of the patients. According to inclusion criteria in the DESIR cohort, this population was characterised by young age (mean age 33.8 years (18–60 years) only three patients older than 50 years) and short duration of axial symptoms (mean 1.6 years). Patients had high disease activity with a mean ADSAS of 3.1 (±1.3) and a mean BASDAI of 4.8 (±2.0); 39.9% had increased CRP (≥6 mg/dl); 28.9% had radiographic sacroiliitis, 20.5% and 36.8% had inflammatory lesions on the spine (thoracic spine 13.5% and lumbar spine 13%) and/or sacroiliac joint MRI, respectively. Fourteen per cent of patients had both sites involved, 6.3% and 22.8% had only spine or sacroiliac lesions, respectively. The mean modified Stoke AS spine score of the studied population was 4.36 (±4.5).

Mean lumbar spine and hip BMD were in the normal range. However, a higher proportion of subjects than expected in such a young population had low BMD (Z≤−2=13.0% and T≤−2=12.7%) at any site. The mean BMD value was lower at lumbar spine (−0.35 g/cm^2) than at total hip (−0.15 g/cm^2, p=0.001). Lumbar spine BMD of patients who had at least one BMO lesion at lumbar spine on MRI was significantly lower than those without (0.98±0.14 vs 1.09±0.17 g/cm^2,

Table 1 Demographic characteristics of the study population according to gender

Variables	Male (n=174)	Female (n=158)	p Value
Age, years (mean±SD)	32.8 (7.8)	34.9 (9.3)	0.037
BMI, kg/m^2 (mean±SD)	24.2 (3.7)	24.0 (4.6)	0.133
Disease duration, years (mean ±SD)	1.6 (1.1)	1.7 (1.0)	0.294
Inflammatory bowel disease (n, %)	9 (5.3%)	11 (7.1%)	0.499
Tobacco use (n, %)	66 (38.4%)	48 (30.6%)	0.137
Alcohol excess (n, %)	39 (22.8%)	7 (4.5%)	<0.0001
HLA-B27 (n, %)	116 (67.4%)	89 (56.3%)	0.038
BAS-G, last week (mean±SD)	4.4 (2.5)	5.3 (2.5)	0.002
ASAS criteria (n, %)	132 (75.9%)	105 (66.5%)	0.058
BASDAI (mean±SD)	3.8 (1.9)	4.8 (2.0)	<0.0001
BASFI (mean±SD)	2.4 (2.0)	3.4 (2.5)	0.0002
BASMI (mean±SD)	1.9 (1.1)	2.1 (1.0)	0.115
CRP, mg/ml (mean±SD)	11.6 (17.9)	7.8 (10.8)	0.988
CRP abnormal, ≥6 mg/dl (n, %)	53 (38.7%)	48 (41.4%)	0.663
ASDAS–CRP (mean±SD)	2.6 (1.1)	2.7 (0.9)	0.236
ESR, mm (mean±SD)	13.3 (17.1)	14.7 (15.0)	0.0002
NSAID use (n, %)	162 (93.1%)	146 (92.4%)	0.806
Radiographical sacroiliitis (n, %)	60 (35.1%)	34 (22.1%)	0.010

ASAS, Assessment of Spondyloarthritis International Society; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BAS-G, Bath ankylosing spondylitis global assessment; BASMI, Bath ankylosing spondylitis metrology index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug.

p=0.0004). Considering the median of age of our population (33.3 years), older subjects (age ≥33.3 years) had a lower lumbar spine BMD (1.1±0.17 vs 1.05±0.16 g/cm^2, p=0.01), a higher BASFI (3.2±2.4 vs 2.6±2.2, p=0.021) and a higher BMI (24.9±4.5 vs 23.4±3.6, p=0.002) but there was no difference for other variables (hip BMD, inflammatory lesions on MRI). Subjects who fulfilled the ASAS criteria had lower lumbar spine BMD (1.06±0.15 vs 1.12±0.18 g/cm^2, p=0.002) and total hip BMD (0.98±0.14 vs 1.02±0.14 g/cm^2, p=0.015); there was no difference for other variables (gender, BASDAI, ADSAS–CRP, BASFI and BASMI) between patients with and without ASAS criteria. Men with ASAS criteria had similar lumbar spine, femoral neck BMD and higher total hip BMD than men without.

Table 2 Bone characteristics of the study population according to gender

Variables	Male (n=174)	Female (n=158)	p Value
Lumbar spine BMD	1.05 (0.17)	1.10 (0.06)	0.019
Lumbar spine Z score	−0.78 (1.25)	−0.10 (1.21)	<0.0001
Lumbar spine T score	−0.74 (1.32)	0.06 (1.16)	<0.0001
Total hip BMD	1.01 (0.14)	0.97 (0.13)	0.002
Total hip Z score	−0.18 (1.03)	−0.03 (1.10)	0.208
Total hip T score	−0.32 (1.09)	0.01 (1.08)	0.020
Femoral neck BMD	0.93 (0.15)	0.92 (0.15)	0.429
Femoral neck Z score	−0.41 (1.05)	−0.05 (1.07)	0.001
Femoral neck T score	−0.66 (1.19)	−0.03 (1.05)	<0.0001
Total lean mass, kg (mean±SD)	55.4 (7.8)	39.6 (5.4)	<0.0001
Total fat mass, kg (mean±SD)	17.8 (9.8)	22.5 (8.1)	<0.0001
% Fat mass (mean±SD)	21.7 (7.4)	34.4 (7.4)	<0.0001
Presence of inflammatory lesions on sacroiliac MRI (n, %)	74 (44.9%)	39 (27.5%)	0.002
Presence of inflammatory lesions on spine MRI (n, %)	39 (23.6%)	24 (16.9%)	0.145
Dorsal inflammatory lesions on spine MRI	28 (17.1%)	13 (9.4%)	0.050
Lumbar inflammatory lesions on spine MRI	24 (14.6%)	13 (9.2%)	0.148

BMD, bone mineral density.

Characteristics of patients with low BMD

Table 3 compares the baseline characteristics of subjects with low bone density (Z≤−2 at any site) and without. Among the

Table 3 Baseline characteristics of patients with low BMD (Z≤-2 at any site)

Variables	Low BMD (N=43)	No Low BMD (N=289)	p Value
Age, years (mean±SD)	32.6 (7.2)	34.0 (8.8)	0.349
Men (N, %)	37 (86.1%)	137 (47.4%)	0<0.0001
Menopause (N,%)	0/6 (0.0%)	7/152 (4.6%)	1.000
BMI, kg/m^2 (mean±SD)	23.0 (3.9)	24.3 (4.2)	0.024
Disease duration, years (mean±SD)	1.83 (1.55)	1.58 (0.94)	0.521
Inflammatory bowel disease (N, %)	4 (9.3%)	8 (2.8%)	0.056
Tobacco use (N, %)	20 (46.5%)	94 (32.9%)	0.080
Alcohol excess (N, %)	7 (16.3%)	39 (13.7%)	0.648
HLA-B27 (N, %)	31 (72.1%)	174 (60.6%)	0.148
BAS-G, last week (mean±SD)	4.95 (2.52)	4.83 (2.53)	0.848
ASAS criteria (N, %)	36 (83.7%)	201 (69.6%)	0.055
BASDAI (mean±SD)	4.34 (2.08)	4.28 (2.04)	0.929
BASFI (mean±SD)	3.00 (2.35)	2.85 (2.33)	0.657
BASMI (mean±SD)	2.28 (1.16)	1.93 (1.08)	0.050
CRP, mg/ml (mean±SD)	20.36 (27.03)	8.14 (11.48)	0.019
CRP abnormal, ≥6 mg/dl (N, %)	19 (54.3%)	82 (37.6%)	0.062
ASDAS–CRP (mean±SD)	3.06 (1.25)	2.55 (0.92)	0.041
ESR, mm (mean±SD)	25.00 (23.89)	12.31 (13.92)	0.0003
NSAID use (N, %)	39 (90.7%)	269 (93.1%)	0.532
Rx sacroiliitis (N, %)	17 (40.5%)	77 (27.2%)	0.077
Inflammatory lesions on sacroiliac MRI (N, %)	23 (56.1%)	90 (33.8%)	0.006
Inflammatory lesions on spine MRI (N, %)	19 (46.3%)	44 (16.5%)	0<0.0001
Dorsal inflammatory lesions on spine (N, %)	13 (31.7%)	28 (10.7%)	0.0003
Lumbar inflammatory lesions on spine MRI (N, %)	11 (26.8%)	26 (9.8%)	0.002
Lumbar spine BMD (mean±SD)	0.86 (0.10)	1.11 (0.15)	0<0.0001
Lumbar spine Z score (mean±SD)	−2.38 (0.63)	−0.06 (1.10)	<0.0001
Lumbar spine T score (mean±SD)	−2.37 (0.79)	−0.06 (1.08)	0<0.0001
Total hip BMD (mean±SD)	0.87 (0.09)	1.01 (0.13)	0<0.0001
Total hip Z score (mean±SD)	−1.24 (0.73)	0.10 (0.99)	<0.0001
Total hip T score (mean±SD)	−1.39 (0.77)	0.02 (1.02)	0<0.0001
Femoral neck BMD (mean±SD)	0.79 (0.10)	0.94 (0.14)	0<0.0001
Femoral neck Z score (mean±SD)	−1.43 (0.75)	0.01 (0.99)	<0.0001
Femoral neck T score (mean±SD)	−1.71 (0.83)	−0.16 (1.08)	0<0.0001
Total lean mass, kg (mean±SD)	51.4 (8.1)	47.3 (10.6)	0.022
Total fat mass, kg (mean±SD)	16.7 (8.3)	20.5 (9.4)	0.009
% Fat mass (mean±SD)	23.4 (8.6)	28.4 (9.7)	0.002

ASAS, Assessment of Spondyloarthritis International Society; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BAS-G, Bath ankylosing spondylitis global assessment; BASMI, Bath ankylosing spondylitis metrology index; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug.

332 patients, a low BMD was measured in 38 (11.5%) patients at the lumbar spine, in 14 (4.2%) at the hip and in 43 (13.0%) patients at both sites.

Univariate analysis showed that variables significantly associated with low BMD (Z≤−2 at any site) were: gender (male) (p<0.0001), ADSAS score (p=0.006), CRP (p=0.0001) and ESR (p<0.0001), the presence of BMO on spine MRI (p≤0.0001) (thoracic (p=0.001) and lumbar levels (p=0.003), on sacroiliac joint MRI (p=0.007), lean mass (0.023) and fat mass (%) (p=0.003) (table 4). There was a significant association between low BMD and the presence of BMO at the spine even in the absence of lesions of the sacroiliac joints (OR 3.09, 95% CI 1.11 to 8.56, p=0.030). However, there was no association with BMO at the sacroiliac joints without BMO at the spine (p=0.795). The variable presence of systemic inflammation (ESR ≥ 20 mm at the first hour or CRP ≥ 6 mg/dl) was significantly associated with low BMD in the univariate analysis (OR 2.68, 95% CI 1.39 to 5.18, p=0.003).

Variables associated with low BMD

Multivariate logistic regression with stepwise selection of variables statistically correlated in univariate analysis showed that the risk factors of low BMD (Z≤−2 at any site) were spine BMO on MRI (OR 4.63, 95% CI 1.90 to 11.31, p=0.001), ESR or CRP (OR 2.60, 95% CI 1.06 to 6.35, p=0.037) and male gender (OR 9.60, 95% CI 2.73 to 33.78, p=0.0004). The AUC for the model was 0.822.

Results of multivariate analysis were similar with the T score definition of low BMD: BMO on MRI (OR 3.59, 95% CI 1.25 to 10.33, p=0.018), ESR or CRP (OR 1.04, 95% CI 1.01 to 1.06, p=0.003) and male gender (OR 34.0, 95% CI 3.92 to 295.42, p=0.001). The AUC for the model was 0.864.

After adjustments for age, weight and centre, multivariate analysis showed that risk factors of low BMD (Z≤−2) were: BMO on MRI (OR 3.56, 95% CI 1.39 to 9.10, p=0.008), ESR (OR 1.03, 95% CI 1.01 to 1.05, p=0.003), male gender (OR 10.16, 95% CI 2.79 to 37.0, p=0.0004). The AUC for the model was 0.823.

Variables associated with low spine or hip BMD

For low spine BMD (Z≤−2), multivariate analysis showed that BMO on MRI was a risk factor (OR 3.30, 95% CI 1.24 to 8.78, p=0.017). The other variables associated with low spine BMD were: ESR (OR 1.03, 95% CI 1.01 to 1.06, p=0.002) and male gender (OR 15.17, 95% CI 3.23 to 71.28, p=0.001) (AUC=0.832). Using the T score, multivariate analysis showed that BMO on MRI was a risk factor for low spine BMD (OR 5.06, 95% CI 1.67 to 15.34, p=0.004). The other variables were: ESR (OR 1.04, 95% CI 1.01 to 1.06, p=0.002) and male gender (OR 24.47, 95% CI 2.91 to 205.69, p=0.003) (AUC=0.880). After adjustments for age, weight and centre, multivariate analysis showed that risk factors associated with low spine BMD were: BMO on MRI (OR 3.02, 95% CI 1.29 to 7.09, p=0.011), ESR (OR 1.03, 95% CI 1.01 to 1.05, p=0.002), male gender (OR 16.53, 95% CI 4.46 to 61.24, p≤0.0001). The AUC for the model was 0.843.

Variables significantly correlated with low hip BMD (Z≤−2) in univariate analysis (p≤0.05) were: male gender (OR 11.29, 95% CI 2.61 to 48.84, p=0.001), BMI (OR 0.88, 95% CI 0.77 to 1.00, p=0.046), the presence of inflammatory lesions on spine MRI (OR 2.55, 95% CI 1.06 to 6.12, p=0.037) and fat mass (%) (OR 0.93, 95% CI 0.88 to 0.98, p=0.004) (table 4). Using the Z score, multivariate analysis showed that spine BMO on MRI was the single risk factor for low hip BMD: OR 8.24, 95% CI 1.98 to 34.30, p=0.004) (AUC=0.736). After adjustments for age, weight and centre, multivariate analysis showed that spine BMO on MRI was a risk factor (OR 7.92, 95% CI 1.84 to 34.07, p=0.005). The AUC for the model was 0.829. None of these variables were significantly associated with low hip BMD in multivariate analysis using the T score.

DISCUSSION

This study conducted in a large cohort of young adults with early IBP suggestive of spondyloarthropathy shows that 13% of patients have a low BMD and that the main risk factors associated with this low BMD are bone and systemic inflammation as assessed by MRI and biological parameters. The presence of

Table 4 Variables associated with low BMD (Z≤-2) in univariate analysis (N=332)

	Low BMD		Low lumbar spine BMD		Low hip BMD	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	0.98 (0.95 to 1.02)	0.346	0.99 (0.95 to 1.03)	0.485	1.00 (0.95 to 1.05)	0.955
Gender (male)	6.84 (3.00 to 18.48)	<0.0001	9.35 (3.24 to 27.01)	<0.0001	11.29 (2.61 to 48.84)	0.001
BMI	0.92 (0.84 to 1.00)	0.061	0.91 (0.83 to 1.01)	0.069	0.88 (0.77 to 1.00)	0.046
BASDAI >40	1.00 (0.53 to 1.93)	0.994	1.10 (0.56 to 2.19)	0.778	0.93 (0.41 to 2.15)	0.871
ASDAS	1.66 (1.15 to 2.38)	0.006	1.70 (1.16 to 2.47)	0.006	1.38 (0.87 to 2.21)	0.175
CRP	1.04 (1.02 to 1.06)	0.0001	1.04 (1.02 to 1.06)	<0.0001	1.01 (0.99 to 1.04)	0.329
ESR	1.04 (1.02 to 1.05)	<0.0001	1.04 (1.02 to 1.06)	<0.0001	1.01 (0.99 to 1.03)	0.288
HLA-B27	0.60 (0.28 to 1.18)	0.152	0.55 (0.26 to 1.17)	0.122	0.66 (0.26 to 1.63)	0.364
ASAS criteria	2.25 (0.97 to 5.26)	0.061	2.32 (0.94 to 5.73)	0.070	1.57 (0.57 to 4.33)	0.385
x-Ray sacroiliitis	1.82 (0.92 to 3.53)	0.080	2.05 (1.02 to 4.13)	0.044	1.25 (0.52 to 3.03)	0.621
Sacroiliac BMO MRI	2.50 (1.28 to 4.87)	0.007	2.72 (1.34 to 5.53)	0.006	1.25 (0.54 to 2.91)	0.608
Spine BMO MRI	4.36 (2.18 to 8.72)	<0.0001	5.02 (2.43 to 10.40)	<0.0001	2.55 (1.06 to 6.12)	0.037
Dorsal spine BMO MRI	3.88 (1.77 to 8.27)	0.001	4.10 (1.86 to 9.07)	0.001	1.78 (0.62 to 5.05)	0.281
Lumbar spine BMO MRI	3.39 (1.52 to 7.54)	0.003	4.15 (1.83 to 9.38)	0.001	2.71 (1.00 to 7.34)	0.0050
Lean mass	1.04 (1.01 to 1.08)	0.023	1.04 (1.01 to 1.08)	0.018	1.04 (1.00 to 1.09)	0.089
Fat mass	0.95 (0.91 to 0.99)	0.017	0.94 (0.89 to 0.98)	0.006	0.97 (0.92 to 1.02)	0.268
% Fat mass	0.95 (0.91 to 0.98)	0.003	0.94 (0.90 to 0.97)	0.001	0.93 (0.88 to 0.98)	0.004

ASAS, Assessment of Spondyloarthritis International Society; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BMD, bone mineral density; BMI, body mass index; BMO, bone marrow oedema; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

BMO lesions on MRI increases the risk of having a low spine BMD threefold.

Low BMD was more frequent at the lumbar spine than at the hip in our population with a short duration of IBP. This population was characterised by young age (mean age 33.8 years) but also a short duration of axial symptoms (mean 1.6 years) due to inclusion criteria (maximum disease duration of 3 years), indicating that the beginning age of symptoms was rather late. In previous studies in long-standing AS, reduced BMD is reflected by low hip BMD; in those studies, the higher lumbar spine BMD is related to an artefactual increase related to either the presence of syndesmophytes[22 23] or the periosteal bone formation (vertebral squaring). Low BMD was observed in 13% of the cohort. We used the Z score to define a low BMD in this young population as it is recommended.[21] Z and T scores were similar at the spine only, but there was a significant difference between these scores at the hip. We are not aware of any study confirming this discrepancy in young adults with IBP.

The high prevalence of low BMD is not explained by traditional risk factors for low BMD (age, low body mass index, smoking…) as we found no difference for these parameters between patients with low BMD and without. In our study, low BMD was more frequent in men, whereas the proportion of women in this cohort was unexpectly high (47.6%). Another study suggests such an association,[24] which could be explained by a higher disease activity in men compared with women; the potential role of sexual hormones in this matter in AS patients remains to be elucidated.[25–27] Nearly half of our patients are women, which is not usual in studies on spondylarthropathies. However, this had been shown previously in other cohorts focusing on patients with early inflammatory back pain.[28 29] In the GESPIC cohort, prevalence of the male gender was 42.9% in non-radiographic axial SpA less than 5 years.[28] In a group of patients with IBP (maximum disease duration 2 years) (the Early SPondyloArthritis Clinic cohort), 62% of subjects were women.[29] The longitudinal follow-up of the patients recruited in the DESIR cohort will allow us to check whether the natural history is gender related or not.

Our study confirms in a large cohort of patients with early IBP that the main risk factor associated with low BMD is the presence of bone (MRI inflammatory lesions) and systemic (ESR or CRP) inflammation.[30] The risk of having a low BMD is increased by the combination of these variables. High levels of interleukin 6 and tumour necrosis factor α have been found in patients with AS with active disease.[11 12] These pro-inflammatory cytokines are involved in bone resorption via the osteoprotegerin/receptor activator for the nuclear factor κB ligand pathway. Anti-tumour necrosis factor α treatments that reduce disease activity can prevent bone loss[31–35] and decrease bone resorption in AS.[31]

This study is the first reporting a significant association between ASDAS–CRP recently validated for assessing disease activity in AS, and low BMD, especially at the lumbar spine. Such an association was not found with BASDAI. These results support the validity of ASDAS–CRP as a measurement instrument for clinical disease activity in early axial SpA. Other AS parameters did not explain low BMD in our study (HLA-B27 antigen, BASFI, presence of chronic inflammatory bowel disease, x-rays sacroiliitis). Mechanical factors, such as stiffness of the spine due to ankylosis are not a likely explanation for low BMD in our group of patients because they were young and had short disease duration. Our study confirms the role of inflammation in bone involvement during inflammatory rheumatism. The presence of BMO on MRI was the main determinant of low BMD in multivariate analysis at both sites. One 1-year longitudinal study in patients with early (less than 2 years) IBP showed that BMD decreased significantly at the hip and not at the lumbar spine in subjects with bone and systemic inflammation markers at baseline (raised CRP and MRI presence of BMO of the sacroiliac joints).[30] In patients with AS, spinal and sacroiliac joint MRI are being used to assess inflammation as an indicator of disease activity; in patients with early IBP a combination of MRI sacroiliitis and HLA-B27 has a high specificity for the future development of AS.[36] Lesions of active inflammation on MRI are depicted as areas of increased signal intensity in T2-weighted images with fat saturation short τ inversion recovery sequences and described as BMO;[37] these lesions are interpreted as inflammatory lesions. One histopathological study conducted in eight patients with AS (age 30–64 years, disease duration 7–33 years) showed a good correlation between the presence of MRI bone oedema of zygapophyseal joints and the histopathological findings (interstitial oedema) but a poor correlation between cell infiltration and bone oedema detected by histology and MRI.[38] However, in this study, cell infiltration was observed in all patients with a greater percentage of confirmed histological interstitial oedema, suggesting that BMO lesions seen on MRI were related to inflammation. Another study comparing AS histology from computed tomography-guided biopsies from the sacroiliac joint with MRI observed some correlation between cell infiltration and BMO by MRI but did not investigate and compare histopathological and MRI BMO.[39] In a study conducted in patients with rheumatoid arthritis scheduled for joint replacement surgery (metacarpophalangeal or proximal interphalangeal joints), with an MRI performed the day before the surgery, bone marrow changes (replacement of bone marrow fat by an inflammatory infiltrate) were correlated with the MRI findings, showing that the presence of BMO reflected true bone marrow inflammation. All these data suggest that BMO on MRI reflect bone inflammation.[40] However, the terminology of BMO on MRI is a misnomer because histologically the abnormality does not correspond to marrow oedema. Taking into account histological findings, even if this terminology is used routinely to describe such lesions, the term of osteitis could be preferred to describe these marrow signal changes in rheumatic diseases.

Our study has limitations. Although the initial cohort was large, the proportion of patients with low BMD was low; thus the relationship between the different sites of bone lesions on MRI and the sites of measurement of BMD should be interpreted with caution. As for all cross-sectional studies, the causality cannot be ascertained above the observations we made. These results must be confirmed by using the prospective data of the DESIR study. Lack of centralised quality control of BMD measurements (ie, use of different devices, absence of cross-calibration) is a limitation of our cross-sectional study; however, centres that participated in this study have an expertise in the field of BMD measurements, and followed the recommendations for quality control of the device.

In conclusion, this study provides evidence that low BMD in patients with IBP is more frequent at the lumbar spine and is the result of bone and systemic inflammation. This emphasises the need for early intervention in AS, especially in patients with inflammatory lesions on MRI.

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Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort

Karine Briot, Anne Durnez, Simon Paternotte, et al.

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Notes