Bone loss in patients with early inflammatory back pain suggestive of spondyloarthritis: results from the prospective DESIR cohort

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Abstract

Objectives. The objectives of the study were to assess the 2 year BMD changes and their determinants in patients with early inflammatory back pain suggestive of axial spondyloarthritis (SpA) (DESIR cohort).

Methods. A total of 265 patients (54% male, mean age 34.4 years) had BMD measurements at baseline and at 2 years. Low BMD was defined as a Z score ≤ −2 (at least one site) and significant bone loss was defined by a decrease in BMD ≥ 0.03 g/cm². Clinical, biological and imaging parameters were assessed over 2 years.

Results. Thirty-nine patients (14.7%) had low BMD at baseline; 112 patients (42.3%) had a 2 year significant bone loss. One hundred and eighty-seven (70.6%) used NSAIDs at baseline and 89 (33.6%) received anti-TNF therapy over 2 years. In anti-TNF users, BMD significantly increased at the lumbar spine and did not change at the hip site from baseline. In multivariate analysis, baseline use of NSAIDs [odds ratio (OR) 0.38, P = 0.006] had a protective effect on hip bone loss. In patients without anti-TNF treatments, baseline use of NSAIDs (OR 0.09, P = 0.006) and a 2 year increase in BMI (OR 0.55, P = 0.003) had protective effects on hip bone loss, whereas a 2 year increase in fat mass was associated with hip bone loss (OR 1.18, P = 0.046).

Conclusion. Among patients with symptoms suggestive of early axial SpA, 42.3% of patients have significant bone loss over 2 years. Anti-TNF therapy is protective against bone loss and baseline use of NSAIDs has a protective effect on hip bone loss.

Key words: spondyloarthritis, bone mineral density, non-steroidal anti-inflammatory drugs, bone, epidemiology.

Introduction

Bone tissue is a target of inflammatory diseases, and bone loss is a complication of persistent inflammation [1]. SpA is associated with bone loss at the spine and the hip [2–7] and an increased risk of vertebral fractures has been reported in AS [8–10]. Attention has been paid recently to a potential association between NSAIDs use and elimination of the excess fracture risk [10]. AS is characterized by osteoproliferation and rigidity of the spine, and part of the vertebral fractures in this disease can be related to the consequences of a decrease in spine mobility [11]. However, low BMD has been reported also in early SpA [12–14]. In patients with recent inflammatory back pain suggestive of early axial SpA, the presence of spinal inflammation diagnosed by bone marrow oedema...
on spinal MRI is significantly associated with low BMD at both the spine and the hip [15]. The aims of this prospective study were to assess the 2 year changes in BMD and to identify the determinants of these changes in a cohort of patients with early inflammatory low back pain. We also investigated the association between BMD changes and the use of drugs effective against inflammation.

Patients and methods

Study population

DESIR (Devenir des spondyloarthrites indifférenciées récentes) is a longitudinal prospective study conducted in 25 centres in France (http://www.lacohortedesir.fr) [16]. Participants provided their written informed consent. Inclusion criteria were adults >18 years but <50 years of age with inflammatory back pain as defined by Calin et al. [17] and/or the Berlin criteria [18] for >3 months but <3 years and symptoms suggestive of SpA according to the local rheumatologist’s assessment. The DESIR study was approved by the French Departmental Directorate of Health and Social Affairs (Directeur Départemental des Affaires Sanitaires et Sociales) and obtained the approval of the appropriate local ethics committees. Patients gave their written consent for use of the collected data in all analyses aiming to answer the objective of the study, therefore no separate ethical approval was required for our study. It was conducted in accordance with the Declaration of Helsinki and the Guidance for Good Clinical Practice (French version, 30 November 2006).

The exclusion criteria were other spinal disease clearly defined (e.g. discarthrosis), a history of any biotherapy and a history of or current disorders that might interfere with the validity of the informed consent and/or prevent optimal compliance of the patient. Corticosteroid intake was permitted only in doses <10 mg equivalent-prednisone/day and had to be stable for at least 4 weeks prior to baseline.

A total of 708 patients in the DESIR cohort were included between October 2007 and April 2010. Patients were classified as having a diagnosis of axial SpA using the Assessment of SpondyloArthritis International Society (ASAS) criteria [19].

Collected parameters

**Clinical parameters and ongoing treatments (assessed at baseline and 6, 12, 18 and 24 months)**

Age, height (m), weight (kg), BMI (kg/m²), risk factors for osteoporosis (tobacco use, alcohol excess and presence of IBD), BASDAI (0–100) and ongoing treatments were assessed at each visit.

The use of NSAIDs was defined as the use of NSAIDs at least once (yes/no), the use of NSAIDs (yes/no) at the time of the assessment and the ASAS NSAID score, which reflects the magnitude of the NSAID intake according to ASAS recommendations [20]. This score takes into account the specific NSAID type, the dose and the percentage of days using NSAIDs. In this study, the ASAS NSAID score was calculated using the last 8 days before the visit. TNF-α inhibitors intake was assessed at each visit and the duration of anti-TNF intake was calculated as the sum of the mean duration of anti-TNF intake reported at each visit.

**Biological parameters**

ESR and CRP were measured at baseline and 6, 12, 18 and 24 months. The ASDAS-CRP has been validated for assessing disease activity in AS [21]. HLA-B27 status was available at baseline. Serum levels of sclerostin (pmol/l) and Dickkopf-1 (DKK-1; pmol/l) were assessed at baseline by sandwich ELISA (Biomedica Medizinprodukte, Vienna, Austria).

**Imaging modalities**

The presence of sacroiliitis was determined on pelvis X-rays. The investigator (local radiologist or rheumatologist) had to rate each sacroiliac joint (normal/doubtful/obvious/fusion) and radiographic sacroiliitis was defined as the presence of obvious lesions of at least one sacroiliac joint.

T1-weighted fast spin echo and short T1 inversion recovery 1–1.5T MRI of the whole spine and the sacroiliac joints were performed to assess inflammatory lesions at baseline. The investigator (local radiologist or rheumatologist) provided binary information: presence of inflammatory lesions (yes/no) at the spinal and sacroiliac level according to the ASAS recommendations.

**BMD measurements**

BMD was measured in all patients by DXA in 12 centres at baseline and 2 years. BMD was determined at the lumbar spine (second–fourth vertebrae) and the upper part of the left femur. The results are given as BMD (g/cm²) and Z scores. Taking into account the age of the studied population, the Z score was determined according to references provided by the manufacturers. Z scores were based on female and male reference curves. Low BMD is defined as Z ≤−2, according to International Society of Clinical Densitometry [22]. BMD changes at 2 years are expressed as a percentage of the baseline value. BMD loss is defined as a significant decrease in BMD at the end of the follow-up period (≥0.03 g/cm² decrease from baseline at the lumbar or total hip site, based on the precision of the measurement at these sites) [23]. Body composition [total lean and fat masses (kg), % fat mass] was measured using DXA from the whole body scan. All exams were performed according to the manufacturer’s recommendations. Devices were controlled by measuring a spine phantom at least three times a week throughout the study; all exams were performed according to the manufacturer’s recommendations.

**Statistical analysis**

Data are expressed as mean (s.d.). Differences in baseline characteristics between patients with baseline and 2 year BMD measurements and patients with only baseline BMD measurements were evaluated using independent t-tests for normally distributed variables, Mann–Whitney U tests for skewed variables and Pearson chi-square tests for dichotomous variables. Within-group changes from...
Baseline in the lumbar spine and hip BMD were assessed as descriptive statistics, with comparisons from baseline values by t-tests or Wilcoxon signed-rank sum tests, as appropriate. BMD changes were also assessed in patients with and without anti-TNF therapy, with comparisons at baseline and between both groups. We tested the interaction between anti-TNF blockers and NSAIDs intake using interaction analysis.

The dependent variable of this study was the bone loss (decrease in BMD >-0.03 g/cm² from baseline) at either lumbar spine or hip. Univariate and multivariate analysis using logistic regression were undertaken using the baseline variables: age, gender, BMI, HLA-B27, BASDAI, ASDAS-CRP, CRP, ESR, current NSAIDs use, ASAS NSAIDs score, X-ray sacroiliitis, bone marrow edema (BME) on sacroiliac or spine MRI, serum sclerostin, serum DKK-1, low BMD (Z ≤−2), lean mass, fat mass, per cent fat mass), treatment with anti-TNF and duration of anti-TNF treatment and longitudinal variables (2 year BMI change, 2 year CRP change, 2 year BASDAI change, 2 year ASDAS-CRP change and 2 year ASAS NSAIDs score). Determinants of 2 year BMD changes were assessed using multivariate logistic regression with stepwise selection and inclusion of variables that had a P-value ≤0.2 in univariate analysis. Because of the effect of anti-TNF therapy on BMD changes, univariate and multivariate analysis were also performed in patients without anti-TNF during the 2 year follow-up. The accuracy of the multivariate models was measured by the area under the curve (AUC). All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the population

BMD was measured in all patients included in 12 centres of the DESIR cohort. BMD data were available in 332 patients at baseline [15]. Thus 265 patients (54% male) with a mean age of 34.4 years had BMD measurements at baseline and 2 years and are the basis of this study. As compared with the 67 patients who had only baseline BMD available, patients included in this prospective study were older (34.4 vs 31.4 years, P = 0.01), had a higher prevalence of HLA-B27 (66.4% vs 48.7%, P = 0.005), had more frequently positive ASAS criteria (79.6% vs 59.5%, P = 0.0004), had more frequently inflammatory lesions on sacroiliac MRI (39.2% vs 24.0%), and reported more frequently a current use of NSAIDs (70.6% vs 50.4%, P = 0.007).

Baseline characteristics

Baseline characteristics are reported in Table 1. Patients had high disease activity with a mean BASDAI of 4.2 (S.D. 1.9) and a mean CRP of 8.2 mg/dl (S.D. 13.2). The use of NSAIDs was reported by 187 patients at baseline (70.6%) with a mean ASAS NSAIDs score of 49.1 (S.D. 43.6). Two hundred and two patients (79.6%) fulfilled the ASAS criteria for axial SpA [19]. Mean lumbar spine and hip BMDs were in the normal range; low BMD (Z ≤−2 at any site) was diagnosed in 39 patients (14.7%).

2 year characteristics

At 2 years, disease activity parameters were significantly lower than at baseline: mean ADSAS 2.0 (S.D. 1.0; P < 0.0001), mean CRP 4.6 (S.D. 4.9; P < 0.0001) and mean BASDAI 3.4 (S.D. 2.2; P < 0.0001) (Table 2). Characteristics of the 2 year visit are reported in Table 2.

2 year BMD changes

Significant but small changes in BMD were measured from baseline over 2 years at the lumbar spine [+1.3% (S.D. 6.4), P = 0.033] and total hip [−0.3% (S.D. 4.0), P = 0.020]. The prevalence of low BMD (Z ≤−2 at least one site) at 2 years was 11.2%. Significant bone loss (BMD >+0.03 g/cm²) was observed in 112 (42.3%) patients, at the lumbar spine only in 22.4% (n = 59) and at total hip only in 18.0% (n = 46). BMI did not significantly change over 2 years. The total fat mass significantly increased from baseline [+6.2% (S.D. 31.0), P = 0.001], whereas appendicular lean mass did not change [3.8% (S.D. 39.7), P = 0.543].

Role of anti-TNF therapy

Eighty-nine patients received anti-TNF during the 2 years because of active disease (Table 1). Among patients with low BMD at baseline, 51.3% (n = 20) received anti-TNF subsequently, as compared with 29.4% (n = 62) in the others (P = 0.0075).

In these 89 patients treated with anti-TNF, lumbar spine BMD significantly increased from baseline [3.2% (S.D. 8.0), P ≤0.001]; there was no significant change in patients without anti-TNF [0.3% (S.D. 5.3), P = 0.70] (P = 0.008 for comparison between groups). Total hip BMD did not significantly change in patients with anti-TNF [0.6% (S.D. 4.1), P = 0.236], whereas it decreased in patients without [−0.8% (S.D. 3.9), P = 0.0001] and the difference between the two groups was significant (P = 0.003) (Fig. 1).

Determinants of bone loss

In the whole population (n = 265)

Univariate analysis showed that parameters significantly associated with significant bone loss (at least one site) were only protective factors: baseline low BMD (Z ≤−2 at any site) [odds ratio (OR) 0.25 (95% CI 0.11, 0.60), P = 0.002], use of anti-TNF treatment [OR 0.53 (95% CI 0.31, 0.90), P = 0.019] and duration of anti-TNF treatment [OR 0.97 (95% CI 0.95, 1.00), P = 0.05]. Parameters significantly associated with significant bone loss at the lumbar spine were age [OR 1.04 (95% CI 1.01, 1.07), P = 0.038], male gender [OR 1.83 (95% CI 1.02, 3.29), P = 0.044], per cent fat mass (for increase of 1 s.d.) [OR 1.04 (95% CI 1.01, 1.07), P = 0.018] and 2 year change of per cent fat mass [OR 1.04 (95% CI 1.01, 1.07), P = 0.018]. Variables associated with significant bone loss at total hip were the use of NSAIDs at baseline [OR 0.44 (95% CI 0.23, 0.86), P = 0.015], baseline low BMD (Z ≤−2 at any site) [OR 0.22 (95% CI 0.05, 0.96), P = 0.043],
2 year BMI increase (for increase of 1 S.D.) [OR 0.88 (95% CI 0.79, 0.98), P = 0.021] and the use of anti-TNF treatment [OR 0.43 (95% CI 0.20, 0.93), P = 0.032]. Neither DKK-1 nor sclerostin serum levels at baseline were associated with significant bone loss at any site.

Among the variables tested in the multivariate analysis [age, male gender, baseline BMI, baseline ESR, baseline low BMD (Z ≤−2), baseline per cent fat mass, use of anti-TNF treatment, duration of anti-TNF treatment], baseline low BMD (Z ≤−2) at any site was the single determinant of bone loss (at least one site) [OR 0.16 (95% CI 0.05, 0.47), P = 0.001]. Among the variables tested (age, male gender, X-ray sacroiliitis, baseline per cent fat mass and 2 year change of per cent fat mass), the only determinant of lumbar spine bone loss was age [OR 1.07 (95% CI 1.01, 1.13), P = 0.020; AUC = 0.665]. Among the variables tested [age, male gender, baseline BMI, baseline CRP, use of NSAIDs at baseline, baseline low BMD (Z ≤−2), 2 year BMI increase and the use of anti-TNF treatment], the current use of NSAIDs at baseline [OR 0.20 (95% CI 0.07, 0.56), P = 0.002; AUC = 0.672] was the single determinant of hip bone loss.

### Table 1 Baseline characteristics of patients with BMD available at baseline (n = 265) with (n = 89) and without anti-TNF (n = 176) during the follow-up

| Variable                              | Total population (n = 265) | Patients without anti-TNF (n = 176) | Patients with anti-TNF (n = 89) | P-value |
|---------------------------------------|---------------------------|-------------------------------------|-------------------------------|---------|
| Age, mean (s.d.)                      | 34.4 (8.7)                | 34.6 (8.6)                          | 33.9 (9.1)                    | 0.5251  |
| Men, n (%)                            | 143 (54.0)                | 79 (44.3)                           | 44 (49.4)                     | 0.4297  |
| BMI, mean (s.d.), kg/m²                | 24.1 (4.1)                | 23.9 (4.0)                          | 24.5 (4.3)                    | 0.3414  |
| Disease duration, mean (s.d.), months | 19.4 (11.2)               | 19.4 (11.3)                         | 19.2 (11.0)                   | 0.9331  |
| IBD, n (%)                            | 10 (3.8)                  | 3 (1.7)                             | 7 (7.9)                       | 0.0339  |
| HLA-B27, n (%)                        | 176 (66.4)                | 131 (75.7)                          | 76 (87.4)                     | 0.6207  |
| ASAS criteria, n (%)                  | 207 (79.6)                | 136 (76.9)                          | 71 (80.9)                     | 0.2802  |
| BASDAI, mean (s.d.)                   | 33.7 (22.0)               | 36.6 (18.5)                         | 53.3 (18.0)                   | <0.0001 |
| BASFI, mean (s.d.)                    | 27.8 (22.5)               | 21.0 (19.0)                         | 40.8 (23.1)                   | <0.0001 |
| CRP, mean (s.d.), mg/ml               | 8.2 (13.2)                | 5.3 (7.2)                           | 13.8 (19.1)                   | <0.0001 |
| ASDAS-CRP, mean (s.d.)                | 2.4 (1.0)                 | 2.1 (0.9)                           | 3.0 (1.0)                     | <0.0001 |
| ESR, mean (s.d.), mm                  | 13.4 (14.8)               | 9.8 (10.0)                          | 20.3 (19.3)                   | <0.0001 |
| Baseline serum DKK-1, mean (s.d.)     | 28.3 (12.8)               | 28.2 (12.2)                         | 28.4 (13.8)                   | 0.6052  |
| Baseline serum sclerostin, mean (s.d.)| 46.4 (24.4)               | 48.0 (24.8)                         | 41.1 (22.7)                   | 0.0643  |
| NSAIDs use, n (%)                     | 247 (93.2)                | 126 (71.6)                          | 61 (69.0)                     | 0.6057  |
| NSAIDs score, mean (s.d.)             | 49.1 (43.6)               | 41.8 (36.1)                         | 63.5 (52.6)                   | <0.0001 |
| Corticosteroids use, n (%)            | 9 (3.4)                   | 5 (2.8)                             | 4 (4.9)                       | 0.4853  |
| Radiographic sacroiliitis, n (%)      | 81 (31.2)                 | 47 (27.0)                           | 34 (39.5)                     | 0.0402  |
| Patients with at least one syndesmophyte, n (%) | 28 (10.6) | 13 (7.4) | 15 (16.8) | 0.1792 |
| Presence of inflammatory lesions on sacroiliac MRI, n (%) | 101 (39.2) | 60 (34.9) | 41 (47.7) | 0.0472 |
| Presence of inflammatory lesions on spine MRI, n (%) | 53 (20.8) | 25 (14.5) | 28 (33.7) | 0.0004 |
| Lumbar spine BMD, mean (s.d.), g/cm²  | 1.07 (0.17)               | 1.08 (0.16)                         | 1.03 (1.00)                   | 0.0300  |
| Lumbar spine Z score, mean (s.d.)     | −0.39 (1.35)              | −0.24 (1.32)                        | −0.69 (1.37)                  | 0.1910  |
| Total hip BMD, mean (s.d.), g/cm²     | 0.99 (0.14)               | 1.00 (0.14)                         | 0.96 (0.13)                   | 0.0122  |
| Total hip Z score, mean (s.d.)        | −0.11 (1.01)              | 0.00 (1.02)                         | −0.32 (0.97)                  | 0.0150  |
| Patients with Z ≤−2, at least one site, n (%) | 39 (14.7) | 19 (11.3) | 20 (4.4) | 0.0075 |
| Total lean mass, mean (s.d.), kg      | 48.1 (10.6)               | 48.8 (10.4)                         | 46.8 (11.0)                   | 0.1584  |
| Total fat mass, mean (s.d.), kg       | 19.9 (9.6)                | 19.3 (9.3)                          | 21.2 (10.1)                   | 0.1190  |
| Per cent fat mass, mean (s.d.)        | 27.4 (8.8)                | 26.0 (9.1)                          | 28.8 (10.9)                   | 0.0391  |

ASAS: Assessment of SpondyloArthritis International Society; DKK-1: Dickkopf-1.

### Table 2 Two-year characteristics of the population

| Variable                              | Value                        |
|---------------------------------------|------------------------------|
| BASDAI, mean (s.d.)                   | 33.7 (22.0)                  |
| CRP, mean (s.d.), mg/ml               | 4.6 (4.9)                    |
| ASDAS-CRP, mean (s.d.)                | 2.0 (1.0)                    |
| ESR, mean (s.d.), mm                  | 9.0 (8.2)                    |
| NSAIDs use, n (%)                     | 172 (64.9)                   |
| Current NSAIDs use at 2 years, n (%)  | 134 (50.6)                   |
| ASAS NSAID score, mean (s.d.)         | 26.8 (37.6)                  |
| Treatment with anti-TNF, n (%)        | 89 (33.6)                    |
| Duration of anti-TNF treatment, mean (s.d.) | 5.7 (9.1)  |
| Incident syndesmophyte, n (%)         | 26 (9.8)                     |
| Presence of inflammatory lesions on sacroiliac MRI, n (%) | 36 (30.5)  |
| Presence of inflammatory lesions on spine MRI, n (%) | 36 (30.5)  |
| Lumbar spine BMD, mean (s.d.), g/cm²  | 1.08 (0.16)                  |
| Lumbar spine Z score, mean (s.d.)     | −0.30 (1.29)                 |
| Total hip BMD, mean (s.d.), g/cm²     | −0.09 (0.98)                 |
| Total hip Z score, mean (s.d.)        | −0.55 (1.67)                 |
| Total lean mass, mean (s.d.), kg      | 48.5 (10.2)                  |
| Total fat mass, mean (s.d.), kg       | 20.1 (9.1)                   |
| Per cent fat mass, mean (s.d.)        | 28.1 (8.5)                   |
In patients without anti-TNF treatment (n = 176)
Multivariate analysis with variables statistically correlated in univariate analysis (age, gender male, baseline percent fat mass, 2 year change of percent fat mass) showed that the single determinant of lumbar spine bone loss was male gender [OR 2.4 (95% CI 1.13, 5.09), P = 0.023; AUC = 0.608]. Among the variables tested (age, male gender, baseline BMI, X-ray sacroiliitis, baseline use of NSAIDs, 2 year increase of BMI and 2 year increase of fat mass), baseline use of NSAIDs [OR 0.09 (95% CI 0.02, 0.50), P = 0.006], 2 year increase in BMI (per 1 s.d. increase) [OR 0.55 (95% CI 0.37, 0.82), P = 0.003] and 2 year increase of fat mass (per 1 s.d. increase) [OR 1.18 (95% CI 1.02, 1.42), P = 0.049; AUC = 0.833] were the determinants of hip bone loss.

Role of NSAIDs
Baseline current use of NSAIDs was protective against hip bone loss in patients with and without anti-TNF therapies in multivariate analysis. Details are reported in Table 3. The ASAS NSAIDs score was similar in patients with and without significant bone loss whatever the site studied. We analysed interactions between anti-TNF and NSAIDs. In this analysis, TNF-α blockers and NSAIDs were independently associated with hip bone loss [OR 0.42 (95% CI 0.2, 0.9) and OR 0.43 (95% CI 0.2, 0.8), respectively]; however, interaction analyses between both treatments did not yield any significant result [OR 0.6 (95% CI 0.1, 2.9), P = 0.52]. TNF-α blockers and NSAIDs were not associated with lumbar spine bone loss; however, interaction analyses between both treatments yielded significant results [OR = 0.2 (95% CI 0.048, 0.856), P = 0.03].

Discussion
This study conducted in a large cohort of young adults with early inflammatory back pain, highly suggestive of axial SpA, shows that BMD is on average in the normal range, but a 2 year BMD loss is measured in 42.3% of the patients. Our study confirms the protective effect of anti-TNF therapy on BMD loss. The baseline current use of NSAIDs and the 2 year BMI increase are protective factors of hip bone loss in these patients, whether or not they receive anti-TNF.

In this population of young adults with early inflammatory back pain, the prevalence of low BMD was 14.7%, and this was higher than expected in young adults; according to normal distribution and the Gauss curve, the expected prevalence in this population is 2.2%. Comparison of this result with previous studies on SpA is difficult due to different definitions of low BMD and to different characteristics of the population. The term ‘early’ can be used differently according to the study; e.g. in the study of van der Weijden et al. [24], early SpA is defined as a diagnosis ≤ 6 months but the mean disease duration was 6 years.

We defined bone loss as a negative change in BMD over the limit of precision of the measurement, and it...
was observed in 42.3% of patients. This could be worrisome if such bone loss is continuous in long-standing disease. However, the relationship between BMD and/or BMD changes and fracture risk is not as well established in secondary osteoporosis as in post-menopausal osteoporosis. Classical risk factors such as age and BMI had an impact on bone loss in our study. Male gender is a risk factor for lumbar spine bone loss. This could be explained by a higher disease activity in men; the potential role of sexual hormones in SpA patients remains to be elucidated [24–26]. Nearly half of our patients are women, which is not usual in studies on SpA. However, this high proportion of women has been shown previously in other cohorts focusing on patients with early inflammatory back pain [27, 28]. A 2 year BMI increase has a protective effect on hip bone loss, confirming the potential positive effect of increased weight on BMD [29]. An increased risk of hip bone loss was observed with an increase in the percentage of fat mass. Whether this relationship could be related to an indirect effect of inflammation on fat mass and/or the secretion by fat tissue of adipokines cannot be elucidated with our available data.

An unexpected result is the role of the Z score on the risk of bone loss: a Z score <−2 at any site was protective of lumbar spine bone loss. This may indicate that bone loss occurred early in some patients, before the occurrence of symptoms, as reported in Crohn’s disease [30], suggesting a deleterious systemic effect of preclinical inflammation.

We analysed the role of inflammation on bone loss, and we showed that the main risk factor associated with low BMD was inflammation imaged by MRI and systemic inflammation [15]. Our prospective analysis does not confirm that baseline inflammation parameters are determinants of bone loss. A 1 year study in 30 patients with early (<2 years) SpA showed that BMD did not change over the follow-up, except in a post hoc analysis of subjects with bone and systemic inflammation markers at baseline [31]. Baseline BME was observed in 39% of our patients at the sacroiliac joints, in contrast to 96.7% of patients in the other study [31]. Moreover, BME is characterized by its variability, thus we cannot state any conclusions about the role of BME at either 1 or 2 years in BMD results.

Drugs effective against inflammation do have an effect on bone loss and may explain this result. One-third of our population received anti-TNF therapy during the 2 year follow-up. We observed in this group a significant increase in lumbar spine BMD over 2 years, in contrast with the absence of changes in the other patients. Similarly, the decrease of hip BMD observed in patients without anti-TNF therapy is not found in patients receiving such treatment. We confirm the positive effects of anti-TNF therapy on BMD previously reported over 6 months [32] and over 2 [33, 34] and 6 years [35]. These BMD changes can be explained by an antiresorptive effect of anti-TNF therapy [36]. Our data suggest that even a short duration of anti-TNF treatment can induce an increase in spine BMD in patients with an inflammatory disorder. Since the BMD increase was observed at the lumbar spine, and not at the hip, this increase could be an artefact related to spinal ossifications (syndesmophytes) or periosteal bone formation (vertebral squaring). However, we previously showed that the long-term lumbar spine BMD changes in patients with severe SpA treated with anti-TNF were similar in patients with and without prevalent and incident syndesmophytes [35].

Finally, a relevant result of our study is the role of NSAIDs on the prevention of bone loss. The use of NSAIDs reported at baseline is a protective factor of hip bone loss, whether or not the patients received anti-TNF therapy during follow-up. However, we did not find any association between the magnitude (dose and duration) of the NSAID intake and BMD changes. Data from a large population-based public health database in Spain show an increased risk of clinical vertebral and non-vertebral fractures among patients with AS, but this excess fracture risk was eliminated by regular use of NSAIDs [10]; however, this result was not confirmed in another study [37]. A positive effect of NSAIDs could be related to a direct bone metabolic effect. NSAIDs might slow the progression of spinal ossification in AS [38–40], delay fracture healing [41, 42] and prevent heterotropic ossification [43]. NSAIDs may act on biological factors such as bone morphogenetic proteins, metalloproteinases and PG receptor genes [44] and may interfere with the Wnt/β-catenin pathway involved in bone formation. Serum DKK and sclerostin levels were not predictive of BMD changes in our study. Since there was no link between the dose of NSAIDs and BMD changes, the effect of NSAIDs may be related to an indirect effect, maybe through physical activity allowed by pain relief, or may only reflect the control of inflammation. In our study, only baseline treatment with NSAIDs was significantly associated with a protective effect on bone loss, suggesting that the bone effect could be related to higher activity at baseline.

Our study has limitations. Although the initial cohort was large, the number of patients with BMD measurements at baseline and 2 years was lower. The lack of centralized quality control of BMD measurements (i.e. use of different devices, absence of cross-calibration) is a limitation of our study; however, centres that participated in this study have an expertise in the field of BMD measurements.

In conclusion, in patients with inflammatory back pain suspicious for early axial SpA followed over 2 years, bone loss occurred in 42.3% of them. Even a short duration of anti-TNF therapy has a positive effect on lumbar spine and hip bone density. Baseline use of NSAIDs is associated with a protective effect on hip bone loss.

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Bone loss in patients with early inflammatory back pain suggestive of SpA

first 5 years. The DESIR cohort is conducted under the control of Assistance publique-Hôpitaux de Paris via the Clinical Research Unit Paris Centre and under the umbrella of the French Society of Rheumatology and Institut national de la santé et de la recherche médicale (Inserm). Database management is performed within the Department of Epidemiology and Biostatistics (Professeur Jean-Pierre Daures, D.I.M., Nîmes, France).

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References

1 Roux C. Osteoporosis in inflammatory joint diseases. Osteoporos Int 2011;22:421–33.
2 Calin A. Osteoporosis and ankylosing spondylitis. Br J Rheumatol 1991;30:318–9.
3 Reid DM, Nicoll JJ, Kennedy NS et al. Bone mass in ankylosing spondylitis. J Rheumatol 1986;13:932–5; Curr Rheumatol Rep 2010;12:332–6.
4 Baek HJ, Kang SW, Lee YJ et al. Osteopenia in men with mild and severe ankylosing spondylitis. Rheumatol Int 2005;26:30–4.
5 El Maghraoui A, Borderie D, Cherrouab B et al. Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. J Rheumatol 1999;26:2205–9.
6 Will R, Palmer R, Bhalla AK, Ring F, Calin A. Osteoporosis in early ankylosing spondylitis: A primary pathological event? Lancet 1989;ii:1483–5.
7 Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology 2001;40:882–8.
8 Cooper C, Carbone L, Michel CJ et al. Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 1994;21:1877–82.
9 Vosse D, Landewé R, van der Heijde D et al. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. Ann Rheum Dis 2009;68:1839–42.
10 Muhoz-Ortego J, Vestergaard P, Rubio JB et al. Ankylosing spondylitis is associated with an increased risk of vertebral and non-vertebral clinical fractures: a population-based cohort study. J Bone Miner Res 2014;29:1770–6.
11 Geusens P, Vosse D, van der Heijde D et al. High prevalence of thoracic vertebral deformities and discal wedging in ankylosing spondylitis patients with hyperkyphosis. J Rheumatol 2001;28:1856–61.
12 Maillefert JF, Aho S, El Maghraoui A, Dougados M, Roux C. Changes in bone density in patients with ankylosing spondylitis: a 2 year follow-up study. Osteoporosis Int 2001;12:605–9.
13 Gratacos J, Collado A, Pons F et al. Significant loss of bone mass in patients with early, active ankylosing spondylitis. A follow-up study. Arthritis Rheum 1999;42:2319–24.
14 Lee YS, Schlotzhauer T, Ott SM et al. Skeletal status of men with early and late ankylosing spondylitis. Am J Med 1997;103:233–41.
15 Briot K, Durnez A, Paternotte S et al. Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort. Ann Rheum Dis 2013;72:1914–9.
16 Dougados M, d’Agostino MA, Benessiano J et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. Joint Bone Spine 2011;78:598–603.
17 Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA 1977;237:2613–4.
18 Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a re-assessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum 2006;54:569–78.
19 Rudwaleit M, van der Heijde D, Landewé R et al. The development of Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial
spondyloarthritis (part II); validation and final selection. Ann Rheum Dis 2009;68:770–6.
20 Dougados M, Simon P, Braun J et al. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis 2011;70:249–51.
21 van der Heijde D, Lie E, Kvien TK et al. ASDAS, a highly discriminatory ASAS endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–8.
22 Lewiecki EM, Gordon CM, Baim S et al. Special report on the 2007 adult and pediatric Position Development Conferences of the International Society for Clinical Densitometry. Osteoporos Int 2008;19:1369–78.
23 Ravaud P, Reny JL, Giraudou B et al. Individual smallest detectable difference in bone mineral density measurements. J Bone Miner Res 1999;14:1449–56.
24 van der Weijden MA, van Denderen JC, Lems WF et al. Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. Clin Rheumatol 2011;30:497–503.
25 Franck H, Meurer T, Hofbauer LC. Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism, and osteoprotegerin serum levels in patients with ankylosing spondylitis. J Rheumatol 2004;31:2236–41.
26 Giltay EJ, Popp-Snijders C, van Schaardenburg D. Serum testosterone levels are not elevated in patients with ankylosing spondylitis. J Rheumatol 1998;25:2389–94.
27 Rudwaleit M, Haibel H, Baraliakos X et al. The early disease stage in axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60:717–27.
28 Heuft-Dorenbosch L, Landewe R, Weijers R et al. Performance of various criteria sets in patients with inflammatory back pain of short duration; the Maastricht early spondyloarthritis clinic. Ann Rheum Dis 2007;66:92–8.
29 Fogelholm GM, Sievänen HT, Kuukkonen-Harjula TK, Pasanen ME. Bone mineral density during reduction, maintenance and regain of body weight in premenopausal, obese women. Osteoporos Int 2001;12:199–206.
30 Roux C, Abitbol V, Chaussade S et al. Bone loss in patients with inflammatory bowel disease: a prospective study. Osteoporos Int 1995;5:156–60.
31 Haugeberg G, Bennett AN, McGonagle D, Emery P, Marzo-Ortega H. Bone loss in very early inflammatory back pain in undifferentiated spondyloarthritis: a 1-year observational study. Ann Rheum Dis 2010;69:1364–6.
32 Visvanathan S, van der Heijde D, Deodhar A et al. Effects of infliximab on markers of inflammation and bone turnover and associations with bone mineral density in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:175–82.
33 Allali F, Breban M, Porcher R et al. Increase in bone mineral density of patients with spondyloarthropathy treated with anti-tumour necrosis factor alpha. Ann Rheum Dis 2003;62:347–9.
34 Briot K, Gossec L, Koltz S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumour necrosis factor-α treatment. J Rheumatol 2008;35:855–61.
35 Durnez A, Paternotte S, Fechtenbaum J et al. Increase in bone density in patients with spondyloarthritis during anti-tumour necrosis factor therapy: 6-year follow-up study. J Rheumatol 2013;40:1712–8.
36 Briot K, Garnero P, Le Henanff A, Dougados M, Roux C. Body weight, body composition, and bone turnover changes in patients with spondyloarthropathy receiving anti-tumour necrosis factor-α treatment. Ann Rheum Dis 2005;64:1137–40A.
37 Prieto-Alhambra D, Muñoz-Ortega J, De Vries F et al. Ankylosing spondylitis confers substantially increased risk of clinical spine fractures: a nationwide case-control study. Osteoporos Int 2015;26:85–91.
38 Wanders A, van der Heijde D, Landewé R et al. Nonsteroidal anti-inflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005;52:1756–65.
39 Kroon F, Landewé R, Dougados D, van der Heijde D. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71:1623–9.
40 Podddubný D, Rudwaleit M, Haibel H et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis 2012;71:1616–22.
41 Konstantinidis I, Papageorgiou SN, Kyrgidis A, Tzellos TG, Kouvelas D. Effect of non-steroidal anti-inflammatory drugs on bone turnover: an evidence-based review. Rev Recent Clin Trials 2013;8:48–60.
42 Kurmis AP, Kurmis TP, O’Brien JX, Dale’ n T. The effect of non-steroidal anti-inflammatory drug administration on acute phase fracture-healing: a review. J Bone Joint Surg Am 2012;94:815–23.
43 Randelli F, Pierannunzii L, Banci L et al. Heterotopic osifications after arthroscopic management of femoroacetabular impingement: the role of NSAID prophylaxis. J Orthop Traumatol 2010;1:245–50.
44 Tuynman JB, Vermeulen L, Boon EM et al. Cyclooxygenase-2 inhibition inhibits c-Met kinase activity and Wnt activity in colon cancer. Cancer Res 2008;68:1213–20.