



Baseline MRI inflammation is not a determinant of 5-year bone mineral density loss in patients with early spondyloarthritis

Marie Fechtenbaum, Anna Molto, Christian Roux, Philippe Goupille, Sylvie Chevret, Karine Briot

► To cite this version:

Marie Fechtenbaum, Anna Molto, Christian Roux, Philippe Goupille, Sylvie Chevret, et al.. Baseline MRI inflammation is not a determinant of 5-year bone mineral density loss in patients with early spondyloarthritis. *Joint Bone Spine*, 2020, 87, pp.63 - 68. <10.1016/j.jbspin.2019.09.016>. <hal-03489954>

HAL Id: hal-03489954

<https://hal.science/hal-03489954v1>

Submitted on 7 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

Baseline MRI inflammation is not a determinant of 5-year bone mineral density loss in patients with early spondyloarthritis

Marie Fechtenbaum^{1,2}, Anna Molto ^{1,2}, Christian Roux^{1,2,3}, Philippe Goupille⁴, Sylvie Chevret⁵, Karine Briot^{1,2}

1.Epidemiology and Biostatistics Unit, Sorbonne Paris Cité Research Center INSERM U1153, Paris, France

2.Department of Rheumatology, Cochin Hospital, Paris, France

3. Paris Descartes University, Paris, France

4. François-Rabelais University, CNRS 7292, Tours, France

5 Biostatistics and Clinical Epidemiology research, INSERM U1153, Paris Diderot University, Paris, France

Corresponding author: Karine Briot, Department of Rheumatology, Cochin hospital, 27 rue du Faubourg saint Jacques 75014 PARIS, +33158412584, karine.briot@aphp.fr

ABSTRACT

Objective: The aim of this study was to assess the effect of baseline inflammation on Magnetic Resonance Imaging (MRI) on the change in Bone Mineral Density (BMD) over 5 years in patients with early spondyloarthritis (SpA).

Methods: From the patients of the DESIR cohort (an early axial SpA cohort), patients with BMD data at both baseline and 5 years, and baseline spine and sacroiliac joints MRI were included. Inflammation was assessed with the SpondyloArthritis Research Consortium of Canada (SPARCC) spine score. Significant BMD loss was defined by a change of $>0.03\text{g/cm}^2$. No patients had received TNF blockers before inclusion in the cohort. Univariate and multivariable prognostic analyses were performed. An inverse propensity score weighting method was used to handle confounders.

Results: One hundred and eighty-three patients were included (mean age 33.9 ± 8.7 years, 58.5 % men). A significant bone loss was reported in 51% (n=92) of patients at either lumbar spine or hip. Fourteen (7%) patients had low BMD (Z-score <-2) at the end of the follow-up vs 28 (15%) at baseline. In multivariable analysis, age was a protective factor of 5 year-BMD loss at any site (OR=0.96, 95% CI [0.93– 0.99]). Baseline MRI inflammation has no significant effect on BMD change at any site (OR= 0.84, 95% CI [0.46–1.53]).

Conclusion: Half of patients with early SpA have a significant bone loss at either lumbar spine or hip over 5 years. Baseline MRI inflammation is not a determinant of this bone loss.

Keywords: early spondyloarthritis, bone mineral density, propensity score, inflammation, osteoporosis

1. Introduction

Osteoporosis is a well-known complication of spondyloarthritis (SpA) (1-5) and has been reported in patients with early disease (6, 7). The prevalence of osteoporosis in these patients typically aged 30-40 years has been reported to be 14–27% and 4–14% at the spine and hip respectively) (3, 6-8) and an increased risk of vertebral fractures has been reported in ankylosing spondylitis (AS) (9).

In SpA, age and Body Mass Index (BMI) (10), male gender (8), presence of syndesmophytes (11), and a sustained inflammation have been showed to be associated with low bone mineral density (BMD) (10, 11). Drugs effective against inflammation do influence bone density (5). Positive effects of TNF blockers on BMD changes have been previously reported over short (6 months) and long term (6 years) follow-up (12-14). These BMD changes can be explained by an antiresorptive effect of TNF alpha blockers therapy, through the control of RANK ligand expression, osteoclastogenesis and osteoclast activity (15).

In a cross-sectional study of patients with recent inflammatory back pain suggestive of early axial SpA (axSpA), presence of inflammation diagnosed by bone marrow oedema on magnetic resonance imaging (MRI) of the spine was significantly associated with low bone mineral density at both the spine and the hip (16).

The objectives of this study were to assess the 5 year-changes in BMD and to assess the impact of baseline MRI inflammation on BMD loss in patients with recent inflammatory back pain suggestive of early axial SpA.

2. Methods

2.1. Study population: the DESIR Cohort

Patients were included from the DESIR (DEvenir des Spondyloarthrites Indifférenciées Récentes) cohort (17) (NCT01648907). DESIR is a French longitudinal prospective cohort including patients from 25 regional centres in France. Patients were over 18 years and under 50 years and reported Inflammatory back pain (IBP) for more 3 months and less 3 years suggestive of early SpA. Written informed consent was filled out by all participants. Steroids intake was permitted only if daily doses of less than 10 mg prednisone and had to be stable for at least 4 weeks before baseline, and no previous TNF alpha blockers use was allowed. A total of 708 patients were included between October 2007 and April 2010.

Study visits occurred every 6 months during the first 2 years of follow-up and yearly thereafter. Data from the first 5 years of follow-up were included in this analysis. Per protocol, twelve of the 25 participating centers performed BMD measurements in all patients at baseline. In this present study, only patients with BMD measurements both at baseline and at 5 years and baseline MRI assessment were included.

2.2. Collected parameters

2.2.1. Clinical parameters and ongoing treatments

At baseline were collected: age (y), Body Mass Index (BMI) (Kg/m^2), risk factors for osteoporosis (current smoking, alcohol intake, presence of inflammatory bowel disease (IBD), last 6-months use of systemic corticosteroids), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI (18), ASDAS-CRP (19) and ongoing treatments. Non-Steroidal Anti Inflammatory Drugs (NSAIDS) intake was defined by the ASAS-NSAID score which reflects the magnitude of the NSAID intake during a given period of time, ranging from 0 to 100, where 100 represents a full NSAID dose during the studied period of time (20). In this study, the ASAS-NSAID score was calculated for the week preceding the visit. Despite at baseline no patients had been exposed to TNF alpha blockers, for this present analysis we considered

that TNF alpha blockers initiation during the first 6 months after inclusion could be considered as baseline use, to be included in the model as predictive “baseline” predictive factors.

2.2.2. Baseline biological parameters

C - reactive protein (CRP) and HLA- *B27* status were assessed.

2.2.3. Central reading of X-rays and MRI:

2.2.3.1. *X-rays*

The spinal structural changes were evaluated by the modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS) and the number of syndesmophytes. The structural damage at the sacroiliac joints was evaluated by the modified New York criteria.

2.2.3.2. *Spine and sacroiliac joint MRI*

All patients underwent at baseline an MRI of the sacroiliac joints and the whole spine, according to a standardized protocol. The SpondyloArthritis Research Consortium of Canada (SPARCC) methods were used for scoring inflammation at the spine and SIJ (21, 22). For scoring of the SIJs, each SIJ was divided into four quadrants. Increased signal intensity on STIR in each quadrant was scored. An additional score of 1 was given if each SIJ on each slice had intense signal. Thus, a patient’s maximum SPARCC score of the SIJs would be 72. For scoring the spine, each discovertebral unit was divided into four quadrants. Additional scores were given if each discovertebral unit on each slice had intense signal or had a signal depth >1 cm. The six discovertebral units with the highest scores were calculated, and a thus patient’s maximum SPARCC score of the spine would be 108 (21, 22). MRI inflammation was defined as a SPARCC score >0 at any site (either SIJ or Spine).

All images were centrally read by 3 experienced readers, who were blinded for clinical data. For binary variables, the scores from the 2 out of 3 agreeing readers were retained, and for continuous variables, the mean of the 3 readers was used.

2.2.4. BMD measurements

BMD was measured by dual-energy x-ray absorptiometry (DXA) at the lumbar spine (second-fourth vertebrae) and the upper part of the left femur. Results were given in g/cm² and Z- score. Low BMD is defined by Z-score ≤ -2 , according to International Society of Clinical Densitometry (23, 24). BMD changes at 5 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 ($>0.03\text{g/cm}^2$ decrease from baseline at the lumbar or total hip site, based on the precision of the measurement at these sites) (23, 24). A significant loss of BMD was defined as a decrease of $>0.03\text{g/cm}^2$ (24) between baseline and 5-year evaluations (24).

All examinations 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 examinations were performed according to the manufacturer's recommendations.

2.3. Statistical analysis

In the main analysis, univariate and multivariate logistic regressions were performed to investigate associations between MRI inflammation at baseline and the presence of significant BMD loss at any site at 5 years. Other variables known to impact the BMD were tested (age, gender, smoking, excess of alcohol intake, BMI, BASDAI, BASFI, baseline CRP, HLA-B27, mSASSS score, NSAIDs score, use of corticosteroids, use of TNF alpha blockers). Multiple logistic regression analyses were performed including all variables selected at the 10% level in univariate analysis.

As a secondary analysis, a statistical approach in causal inference based on propensity score (PS) (25) was used to assess the causal impact of the MRI inflammation when handling confounders measured at baseline, including the TNF alpha blockers use, as several studies reported the positive effect of TNF alpha blockers on BMD loss (12, 14, 16, 26). In our setting, the PS was defined by the probability to present an MRI inflammation (e.g. a SPARCC >0) at baseline. It allowed obtaining comparable groups that would only differ based on the presence/not presence of MRI inflammation. First, we measured baseline imbalances between patients without and with inflammation by the observed standardized mean differences (SMD) (threshold of 0.10) (27). The PS was estimated by multivariable logistic regression including the imbalanced and prognostic variables that have been reported in the literature to have an impact on bone loss (28). Several PS models were tested and compared (based on the SMD, C-index, and the overlap and distribution of quintiles) (29-31). Finally, the PS included the NSAIDs score (20, 32), TNF alpha blockers, BMI, age and gender. Inverse probability of weights (IPW) was then used to create a pseudo population in which the MRI inflammation is independent of the measured confounders. Similar analyses were performed to assess the impact of MRI inflammation on lumbar spine and total hip BMD changes. All analyses were performed with R-CRAN software, R-3.2.4.

3. Results

3.1. Characteristics of patients at baseline

BMD measurements were performed at baseline for 340 patients. As shown on figure 1, 183 patients (mean age of 33.9 ± 8.7 years, 58.5% of men) had both BMD measurements at baseline and at 5 years and a MRI at baseline and are the basis of this study. Mean duration of symptoms was 78.4 ± 44.7 weeks. Characteristics of these 183 patients are reported in table 1. Compared to characteristics of 708 patients included in the DESIR cohort, a significant

difference was found for gender (SMD =0.312), age (SMD=0.034), BMI (SMD =0.034), NSAIDs score (SMD=0.054) and use of TNF alpha blockers during the 6 months following the inclusion in the cohort (SMD=0.087) were similar. At baseline low BMD at any site was observed in 15 patients (28%).

Sixty-three percent (n=115) patients had inflammation on MRI (SPARCC score >0 at any site, 3.3 (7.1%) at the SIJ and 2.9 (9.2%) at spine). Baseline characteristics of patients with/without MRI inflammation are in Table 1.

3.2. 5-year BMD changes

The mean change in BMD over 5 years was $+2.59 \pm 8.8\%$ and $-0.50 \pm 4.95\%$ at the lumbar spine and hip, respectively. A significant bone loss ($> 0.03\text{g/cm}^2$) was measured at either lumbar spine, or total hip in 92 (51%) of patients (n=34 at lumbar spine (19%), and 47 (26%) at total hip). In contrast, a significant increase in BMD (i.e. $>0.03\text{ g/cm}^2$) was observed at lumbar spine in 66 patients (36%) and total hip in 29 patients (16%). 28 patients (15%) had a low BMD at baseline (i.e. Z-score <-2 at any site) and 14 (7%) patients at 5 years. In those with baseline low BMD ($Z \leq -2$ at at least one site) BMD significantly increased at lumbar spine ($+7.4 \pm 14.3\%$) and total hip ($+1.2 \pm 7\%$) over 5 years. Baseline characteristics of patients in study population, according to the presence of significant bone loss at any site over 5 years are in Table 2.

3.3. Impact of baseline MRI inflammation on BMD loss at any site over 5 years (Main analysis)

3.3.1. Univariate and multivariable analyses

In the univariate analysis, baseline age (OR= 0.97, 95% CI [0.93– 0.99], $p=0.065$), BASDAI (OR=0.98, 95% CI [0.93 – 0.99], $p=0.015$), BASFI (OR= 0.97, 95% CI [0.96 – 0.99],

p=0.016), CRP (OR= 0.96, 95% CI [0.93-0.99]), p=0.019) and TNF alpha blockers use (OR= 0.46, 95% CI [0.22 -0.93], p=0.04) were inversely associated with bone loss at any site. Baseline MRI Inflammation (SPARCC >0) was not associated with BMD loss at any site at 5 years (OR= 0.84, 95% CI [0.46–1.53], p=0.70). Presence of existing/new syndesmophytes was not associated with BMD loss (OR=0.56, 95% CI [0.21 -1.41], p=0.325) at any site. In multivariable analysis, age was the single variable associated with a significant BMD loss at 5 years with a protective effect (OR=0.96, 95% CI [0.93– 0.99]).

3.3.2. Inversed probability weighting by propensity to MRI inflammation.

Standardized mean differences of the covariates after weighting were significantly reduced (data not shown). After application of the weights, baseline MRI inflammation was not associated with BMD loss at 5 years (OR= 0.83, 95%CI [0.44-1.55]).

3.4. Impact of MRI inflammation on lumbar spine and total hip bone loss over 5 years (secondary analyses)

In univariate logistic regression, one unit decreased smoking was the only variable associated to a significant bone loss at the lumbar spine (OR= 0.96, 95% CI [0.45 -0.97], p=0.007). In multivariable analysis, no variable was associated with significant lumbar spine BMD over 5 years.

In univariate analysis, decreased age (OR= 0.92, 95% CI [0.88 – 0.96], p<0.001), decreased BASDAI (OR= 0.97, 95% CI [0.96-0.99], p=0.02), decreased BASFI (OR= 0.98, 95% CI [0.96 -0.99], p=0.02) and decreased CRP (OR= 0.95, 95% CI [0.90 –0.99], p=0.007) were associated with significant total hip BMD loss. In multivariable analysis, only age and CRP

were retained as protective factors of significant total hip BMD loss (OR= 0.91, 95% CI [0.87 -0.96] and (OR= 0.95, 95% CI [0.89 -0.99], respectively.

In inverse probability of weight analysis, baseline MRI inflammation had no significant effect on BMD at lumbar spine (OR= 1.21, 95%CI [0.54-2.73]) and total hip (OR= 1.19, 95%CI [0.58-2.46]).

4. Discussion

This prospective study failed to show any predictive role of baseline inflammation measured by a spine and sacroiliac joints MRI on BMD loss over 5 years in patients with recent inflammatory back pain suggestive of early axial SpA. Our study shows the high prevalence of a 5-year bone loss measured in 51% of these young patients. We also confirm the protective effect of TNF blockers on bone loss at 5 years in univariate analysis.

We previously showed in the same cohort that 42.3% of patients had a significant BMD loss (using the same definition) over 2 years (28). This could be worrisome if such a bone loss is continuous in long-standing disease. Our study shows that the prevalence of bone loss is similar at 2 and 5 years: 42.3% (28) and 51% of patients respectively), suggesting that most of BMD loss occurs early in axSPA. Moreover, the magnitude of BMD changes in the whole studied population remains on average small at 2 years (+1.3% and -0.3%) and at 5 years (+2.6% and -0.6%) at spine and total hip, respectively. There is no prospective data assessing the role of such small changes on fracture risk in ax SPA.

We analyzed the determinants of bone loss, at both spine and hip, considering the usual osteoporosis risk factors (such as gender, BMI) and the characteristics of the inflammatory disease and its treatments. Among the classical risk factors for bone loss, age was the single one which had a significant impact on bone loss with a protective effect. But we did not find

any association between male gender, or BMI as in previous studies (32). As in previous studies, we found a decrease in total hip BMD (33, 34). Surprisingly, baseline high CRP was found to be protective for hip bone loss at 5 years. These results contrast with previous studies which showed a more pronounced decrease in femoral neck BMD in patients with high ESR during follow-up (35, 36). In these studies, patients did not receive TNF blockers, and our hypothesis is that use of these treatments in our population prevents inflammation-related bone loss. As in the 2-year analysis, we showed that the use of anti TNF alpha was a protective factor of BMD loss at both spine and hip in univariate analysis (28), recognizing that our study was not designed to demonstrate the impact of anti TNF alpha on BMD; this parameter was included as a confounding factor. Moreover, these results concern baseline CRP value and we did not study the relation between BMD changes and CRP over time

One longitudinal study, conducted in 204 Swedish patients with ankylosing spondylitis (50 ± 13 years old), over 5 years showed that BMD decreased significantly at the femoral neck and increased significantly at the lumbar spine (33). But this study was conducted in patients with a long disease duration (24 years). In this study, increase in lumbar spine BMD was explained by both the use of TNF blockers, the use of bisphosphonates and by the syndesmophyte formation. In our study conducted in patients with early disease, lumbar spine BMD significantly increased in 36% of patients whereas few patients had a spine structural involvement at baseline (mean mSASSS score of 0.584). Moreover, the increase in lumbar spine BMD cannot be explained by the occurrence of syndesmophytes as the structural progression is weak in the DESIR cohort (mean value mSASSS at 2 years of 0.27) (37). In our study, none of the patients received bisphosphonates over the follow up. Thus, our hypothesis is that the inflammation control (by TNF blockers) explains the increase in lumbar spine BMD.

In our study, the absence of impact of baseline MRI inflammation was confirmed with the PS-weighting analysis, performed to handle carefully confounders of BMD loss to identify its causal impact. We chose to assess MRI inflammation by the SPARCC score, validated in SpA (21, 22). However, our result might be very likely explained by the low values of the score, and we did not find any difference even after truncation sensitivity analysis using a more relevant threshold of a SPARCC > 2 since a score of 1 and 2 may be due to an artefact (data not shown). The mean values of SPARCC score were low as compared to other studies. In a study of 106 patients with a non-radiographic SpA taking etanercept for less than 5 years, the mean SPARCC Spine score was 4.7 (38). Likewise, in the SPACE study, 60 patients with <2 years SpA had a mean SPARCC Spine score and SPARCC SIJ score of 7.26, 15.35 in radiographic group and 5.18, 12.53 in non-radiographic group, respectively (39). With an anti TNF alpha treatment, a minimally important change for the SPARCC spine score was proposed to be 5.0 by Maksymovych et al (40). In our study, the difference between the 2 groups with and without significant bone loss was only 1.8 and the clinical relevance of this difference is unknown. Our results could be explained by the characteristics of the patients of the DESIR cohort with a lower disease duration than patients included in other studies (11, 41). Moreover, the early and optimal management of SpA patients with tight control of inflammation which is now recommended could explain the low value of SPARCC and our results.

Methodological issues, such as violation of model specification must be discussed. Confounding factors need to be chosen related to the outcome and avoiding those only associated to the exposure. Even if we have included confounding factors based on previous studies and expert opinion, the strength of their association to MRI inflammation could have been minimized and induced an increase of bias. In this way, we have assessed the impact of several other covariates to create PS but without marked difference between models (data not

shown). However, we cannot exclude that some confounding covariates at baseline have not been measured.

This study is the first in a cohort of patients with very early disease, assessing the impact of MRI inflammation at baseline on the BMD loss on a long-term follow-up (5 years). There were only three missing data regarding our confounders and this increases the robustness of our PS-weighting analyses. However, our study has some limitations. Although the initial cohort was large, the number of patients with BMD measurements at baseline and 5 years was lower, and we could not exclude some selection bias. Lack of centralized quality control of BMD measurements (i.e. use of different devices, absence of cross-calibration) is another limitation of our study; however, centres which participated in this study have an expertise in the field of BMD measurements. Finally, we hypothesized that BMD changes can be related to change in MRI inflammation over time, but only 70 patients performed MRI at 5 years in the cohort.

In conclusion, in patients with recent inflammatory back pain suggestive of early axial SpA, 51% of patients have a BMD loss at any site at 5 years. There was no evidence that baseline MRI inflammation is a determinant of this BMD loss at any site at 5 years.

Acknowledgements:

The DESIR study is conducted as a Programme Hospitalier de Recherche Clinique with Assistance Publique Hopitaux de Paris as the sponsor. The DESIR study is also under the umbrella of the French Society of Rheumatology, which financially supports the cohort. An unrestricted grant from Pfizer has been allocated for the first 5 years. The DESIR cohort is conducted under the control of Assistance publique Hopitaux de Paris via the Clinical

Research Unit Paris Centre and under the umbrella of the French Society of Rheumatology and Institut national de la sante et de la recherche medicale (Inserm). Database management is performed within the Department of Epidemiology and Biostatistics (Professeur Jean-Pierre Daures, D.I.M., Nîmes, France). We also wish to thank the different regional participating centres: Pr Maxime Dougados (Paris-Cochin B), Pr Andre Kahan (Paris-Cochin A), Pr Philippe Dieudé (Paris-Bichat), Pr Bruno Fautrel (Paris-La Pitie-Salpetriere), Pr Francis Berenbaum (Paris-Saint-Antoine), Pr Pascal Claudepierre (Creteil), Pr Maxime Breban (Boulogne-Billancourt), Dr Bernadette Saint-Marcoux (Aulnay-sous-Bois), Pr Philippe Goupille (Tours), Pr Jean Francis Maillefert (Dijon), Dr Emmanuelle Dernis (Le Mans), Pr Daniel Wendling (Besancon), Pr Bernard Combe (Montpellier), Pr Liana Euller-Ziegler (Nice), Pr Pascal Richette (ParisLariboisiere), Pr Pierre Lafforgue (Marseille), Dr Patrick Boumier (Amiens), Pr Martin Soubrier (ClermontFerrand), Dr Nadia Mehzen (Bordeaux), Pr Damien Loeuille (Nancy), Pr Rene-Marc Flipo (Lille), Pr Alain Saraux (Brest), Pr Xavier Mariette (LeKremlin-Bicetre), Pr Alain Cantagrel (Toulouse), Pr Olivier Vittecoq (Rouen). We wish to thank the research nurses, the staff members of the Clinical Research Unit of Paris Centre, the staff members of the Biological Resource Center of Bichat Hospital, the staff members of the Department of Statistics of Nîmes and all the investigators, and in particular Jerome Allain, Emmanuelle Dernis, Salah Ferkal, Clement Prati, Marie-Agnes Timsit, Eric Toussirot for active patient recruitment and monitoring.

Disclosure statement: C.R. has received research grants and/or honoraria from Alexion, Amgen, Bongrain, Lilly and MSD. All other authors have declared no conflicts of interest.

References

1. Roux C. Osteoporosis in inflammatory joint diseases. *Osteoporos Int* 2011; 22:421–33.
2. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *JAMA* 1977;237:2613–4.
3. El Maghraoui A, Borderie D, Cherruau B, Edouard R, Dougados M, Roux C. Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. *J Rheumatol* 1999 ;26:2205–9.
4. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O’Fallon WM, Melton LJ. Fracture risk in patients with ankylosing spondylitis: a population based study. *J Rheumatol* 1994 ;21:1877–82.
5. Briot K, Geusens P, Em Bultink I, Lems WF, Roux C. Inflammatory diseases and bone fragility. *Osteoporos Int* 2017;28:3301–14.
6. Will R, Palmer R, Bhalla AK, Ring F, Calin A. Osteoporosis in early ankylosing spondylitis: a primary pathological event? *Lancet* 1989;2:1483–5.
7. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. *Rheumatol* 2001;40:882–8.
8. Ghoulani I, Ghazi M, Nouijai A, Mounach A, Rezqi A, Achemlal L, et al. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone* 2009 ;44:772–6.
9. Briot K, Roux C. Inflammation, bone loss and fracture risk in spondyloarthritis. *RMD Open*. 2015 ;1:e000052
10. Klingberg E, Lorentzon M, Mellström D, Geijer M, Göthlin J, Hilme E, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Res Ther*. 2012;14:R108.
11. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol* 2005; 32:1290–8.
12. Briot K, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-alpha treatment. *J Rheumatol* 2008 ;35:855–61.
13. van der Weijden M a. C, van der Horst-Bruinsma IE, van Denderen JC, Dijkmans B a. C, Heymans MW, Lems WF. High frequency of vertebral fractures in early spondylarthropathies. *Osteoporos Int* 2012;23:1683–90.
14. Durnez A, Paternotte S, Fechtenbaum J, Landewé RBM, Dougados M, Roux C, et al. Increase in Bone Density in Patients with Spondyloarthritis During Anti-Tumor Necrosis

Factor Therapy: 6-year Follow-up Study. *J Rheumatol*. 2013;40:1712–8.

15. 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;64:1137–40.

16. Briot K, Durnez A, Paternotte S, Miceli-Richard C, Dougados M, Roux C. 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.

17. Dougados M, Etcheto A, Molto A, Alonso S, Bouvet S, Daurès JP, Landais P, d'Agostino MA, Berenbaum F, Breban M, Claudepierre P, Combe B, Fautrel B, Feydy A, Goupille P, Richette P, Pham T, Roux C, Treluyer JM, Saraux A, van der Heijde D, Wendling D; DESIR cohort. Clinical presentation of patients suffering from recent onset chronic inflammatory back pain suggestive of spondyloarthritis: The DESIR cohort. *Joint Bone Spine* 2015; 82: 345-51.

18. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286–91.

19. Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18–24.

20. Dougados M, Simon P, Braun J, Burgos-Vargas R, Maksymowych WP, Sieper 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. Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Krishnananthan R, Stone M, et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005 15;53: 502–9.

22. Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Williams M, Stone M, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005 ;53:703–9.

23. Lewiecki EM, Gordon CM, Baim S, Binkley N, Bilezikian JP, Kendler DL, 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.

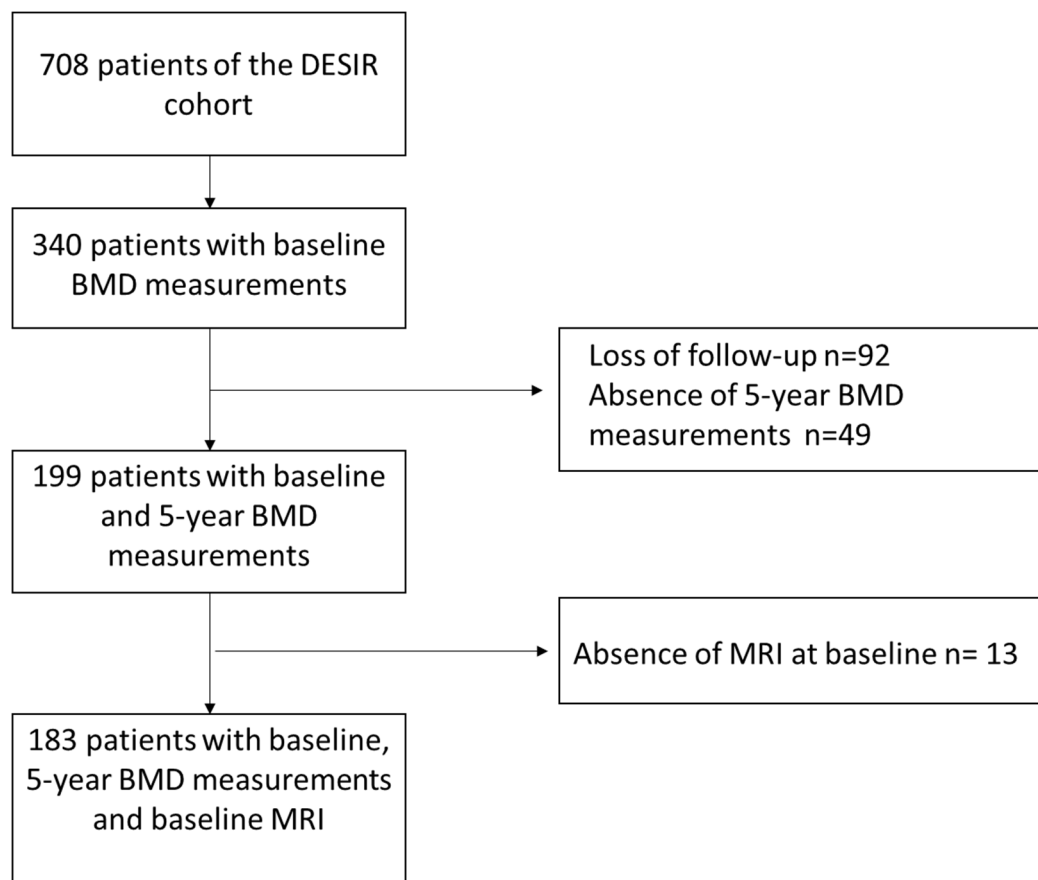
24. Ravaud P, Reny JL, Giraudeau B, Porcher R, Dougados M, Roux C. Individual smallest detectable difference in bone mineral density measurements. *J Bone Miner Res* 1999 14:1449–56.

25. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivar Behav Res* 2011 ;46:399–424.

26. van der Weijden MAC, van Denderen JC, Lems WF, Nurmohamed MT, Dijkmans BAC, van der Horst-Bruinsma IE. Etanercept Increases Bone Mineral Density in Ankylosing Spondylitis, but Does Not Prevent Vertebral Fractures: Results of a Prospective Observational Cohort Study. *J Rheumatol* 2016 ;43:758–64.
27. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387–98.
28. Briot K, Etcheto A, Miceli-Richard C, Dougados M, Roux C. Bone loss in patients with early inflammatory back pain suggestive of spondyloarthritis: results from the prospective DESIR cohort. *Rheumatology* 2016;55:335–42.
29. Wyss R, Girman CJ, LoCasale RJ, Brookhart MA, Stürmer T. Variable Selection for Propensity Score Models When Estimating Treatment Effects on Multiple Outcomes: a Simulation Study. *Pharmacoepidemiol Drug Saf* 2013;22:77–85.
30. Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. *J Clin Epidemiol* 2006;59:437–47.
31. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107.
32. Giltay EJ, van Schaardenburg D, Gooren LJ, Popp-Snijders C, Dijkmans BA. Androgens and ankylosing spondylitis: a role in the pathogenesis? *Ann N Y Acad Sci* 1999; 22;876:340–364.
33. Deminger A, Klingberg E, Lorentzon M, Geijer M, Göthlin J, Hedberg M, et al. Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. *Arthritis Res Ther* 2017;19:273.
34. Kaya A, Ozgocmen S, Kamanli A, Ardicoglu O. Bone loss in ankylosing spondylitis: does syndesmophyte formation have an influence on bone density changes? *Med Princ Pract.* 2009;18:470-6.
35. Gratacos J, Collado A, Pons F, Osaba M, Sanmarti R, Roque M. Significant loss of bone mass in patients with early, active ankylosing spondylitis: a follow-up study. *Arthritis Rheum.* 1999;42):2319–24.
36. Haugeberg G, Bennett AN, McGonagle D, Emery P, Marzo-Ortega H. Bone loss in very early inflammatory back pain in undifferentiated spondyloarthropathy: a 1-year observational study. *Ann Rheum Dis* 2010;69:1364–6.
37. Ramiro S, Heijde D van der, Berg R van den, Navarro-Compán V, Feydy A, D’Agostino MA, et al. FRI0234 Spinal Radiographic Progression in Early Axial Spondyloarthritis: Data from the Desir Cohort. *Ann Rheum Dis.* 2015 ;74(Suppl 2):509–509.

38. Dougados M, van der Heijde D, Sieper J, Braun J, Citera G, Lenaerts J, van den Bosch F, Wei JC, Pedersen R, Bonin R, Jones H, Marshall L, Logeart I, Vlahos B, Bukowski JF, Maksymowych WP. Effects of Long-Term Etanercept Treatment on Clinical Outcomes and Objective Signs of Inflammation in Early Nonradiographic Axial Spondyloarthritis: 104-Week Results From a Randomized, Placebo-Controlled Study. *Arthritis Care Res (Hoboken)* 2017;69:1590-1598.
39. van den Berg R, de Hooze M, Bakker PAC, van Gaalen F, Navarro-Compán V, Fagerli KM, et al. Metric Properties of the SPARCC Score of the Sacroiliac Joints - Data from Baseline, 3-month, and 12-month Followup in the SPACE Cohort. *J Rheumatol* 2015;42:1186–93.
40. Maksymowych WP, Lambert RG, Brown LS, Pangan AL. Defining the Minimally Important Change for the SpondyloArthritis Research Consortium of Canada Spine and Sacroiliac Joint Magnetic Resonance Imaging Indices for Ankylosing Spondylitis. *J Rheumatol*. 2012;39:1666–74.
41. van der Weijden M a. C, Claushuis T a. M, Nazari T, Lems WF, Dijkmans B a. C, van der Horst-Bruinsma IE. High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clin Rheumatol* 2012 ;31:1529–35.

Figure 1: Study Flow-chart



BMD: Bone mineral density

Table 1: Baseline characteristics of patients in study population, according to the presence of MRI inflammation at baseline.

Characteristics baseline	Total N=183	MRI Inflammation at baseline*		
		no N=115	yes N=68	SMD
Age, m (S.D.)	33.9 (8.7)	34.5 (8.0)	33.5 (9.1)	0.11
Men, n (%)	107 (58.5)	34 (50)	73 (63)	0.27
BMI, m (S.D), kg/m ²	24.1 (3.8)	24.5 (3.7)	23.8 (3.9)	0.18
Disease duration, m (S.D),w	78.4 (44.7)	74.7(47.1)	80.6 (43.3)	0.13
Extra-articular manifestations n (%)	62 (34)	17 (25)	45 (39)	0.31
Current smoking n (%)	65 (35.5)	54 (79)	64 (56)	0.52
<i>HLAB-27</i> + n (%)	126 (68.8)	47 (69)	79 (69)	0.01
BASDAI m (S.D.)	40.1 (19.9)	39.9 (20.9)	40.2 (19.3)	0.01
BASFI m (S.D.)	26.3 (22.1)	25.8 (21.3)	26.6 (22.6)	0.04
CRP m (S.D.) mg/L	7.8 (12.3)	5.29 (6.89)	9.33 (14.30)	0.36
ASDAS CRP m (S.D.)	2.4 (0.9)	2.40 (0.99)	2.46 (0.98)	0.06
NSAID score m (S.D.)	45.9 (37.1)	44.17 (34.47)	47.05 (38.72)	0.08
Last 6 months corticosteroids use n (%)	27 (14.8)	57 (84)	99 (86)	0.06
TNF alpha blockers initiation during the 6 months following the inclusion in the cohort (%)	42(23)	14 (20.6)	28 (24.3)	0.09
Presence of low BMD (Z-score \leq -2 at least one site) n (%)	28(15)	5 (7)	23 (20)	0.37

Lumbar spine BMD m (S.D.) g/cm ²	1.072 (0.169)	1.09 (0.18)	1.06 (0.16)	0.21
Lumbar spine Z-score \leq -2 n (%)	24 (13)	4 (5.9)	20 (17.4)	0.36
Total hip BMD m (S.D.) g/cm ²	0.996(0.137)	1.00 (0.14)	0.99 (0.14)	0.05
Total hip Z-score \leq -2 n (%)	6 (3.4)	1 (2)	5 (4)	0.17
Radiographic sacroiliitis n (%)	24 (13.4)	4 (6)	20 (18)	0.37
mSASSS m (S.D.)	0.584(2.099)	0.41 (1.04)	0.69 (2.52)	0.14
SPARCC Spine score m (S.D.)	2.9 (9.2)	0.00 (0.00)	4.54 (11.28)	0.57
SPARCC SIJ score m (S.D.)	3.3 (7.1)	0.01 (0.08)	5.10 (8.31)	0.87

*: defined by a SPARCC Spine >0 or SPARCC SIJ >0;

‰: percent, ASDAS- CRP: Ankylosing Spondylitis Disease Activity Score with CRP, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BMD: bone mineral density, BMI: body mass index, CRP: C reactive protein, m: mean, mny: modified new York criteria, mSASSS: modified Stokes Ankylosing Spondylitis Spinal Score, n: number, NA: not applicable, NSAIDs score: non-steroidal anti-inflammatory drugs, SPARCC SIJ: SpondyloArthritis Research Consortium of Canada sacroiliac joint, SPARCC Spine: SpondyloArthritis Research Consortium of Canada spine, S.D: standard deviation, SMD: standardized mean difference, w weeks.

Table 2: Baseline characteristics of patients in study population, according to the presence of significant bone loss at any site over 5 years.

Characteristics baseline	N	Total N=183	Significant loss of BMD at any site at 5 years		
			no N=91	yes N=92	SMD
Age, m (S.D.)	183	33.9 (8.7)	35.1(9.1)	32.7(8.2)	0.27
Men, n (%)	183	107 (58.5)	50 (55)	57 (62)	0.14
BMI, m (S.D), kg/m ²	183	24.1 (3.8)	24.55 (4.3)	23.66(3.2)	0.23
Disease duration, m (S.D),w	183	78.4 (44.7)	73.3 (45.8)	83.5 (43.3)	0.23
Extra-articular manifestations n (%)	183	62 (34)	32 (35)	30 (33)	0.05
Current smoking n (%)	182	65 (35.5)	55 (59)	61 (68)	0.06
<i>HLAB-27</i> + n (%)	183	126 (68.8)	60 (66)	66 (71)	0.13
BASDAI m (S.D.)	183	40.1 (19.9)	43.7 (19.3)	36.5 (20)	0.36
BASFI m (S.D.)	182	26.3 (22.1)	30.3(22.9)	22.4 (20.6)	0.36
CRP m (S.D.) mg/L	176	7.8 (12.3)	10.1 (13.4)	5.73 (10.1)	0.35
ASDAS CRP m (S.D.)	172	2.4 (0.9)	2.6 (1.0)	2.2 (0.9)	0.46
NSAID score m (S.D.)	180	45.9 (37.1)	45.9 (36.25)	46.0(38.2)	0.002
Last 6 months steroids use n (%)	183	27 (14.8)	15 (17)	12(13)	0.09
Use of Anti TNF α treatment at 6 months n (%)	183	42 (23)	27 (30)	15 (16)	0.32
Presence of low BMD (Z-score \leq -2 at least one site) n (%)	183	28 (15)	17 (19)	11 (12)	0.18
Lumbar spine BMD m (S.D.) g/cm ²	183	1.072 (0.169)	1.061 (0.182)	1.093 (0.162)	0.16
Lumbar spine Z-score \leq -2 n (%)	182	24 (13)	16 (17)	8 (9)	0.26
Total hip BMD m (S.D.) g/cm ²	179	0.996 (0.137)	0.971 (0.141)	1.021 (0.131)	0.34

Total hip Z-score ≤ -2 n (%)	175	6 (3.4)	2 (2)	4 (4)	0.12
Radiographic sacroiliitis mny n (%)	179	24 (13.4)	16 (18)	8 (9)	0.27
mSASS m (S.D.)	176	0.584 (2.099)	0.701 (2.241)	0.472 (1.963)	0.11
SPARCC Spine score m (S.D.)	183	2.9 (9.2)	3.73(9.10)	1.99(9.24)	0.20
SPARCC SIJ score m (S.D.)	179	3.3 (7.1)	2.80 (5.65)	3.77 (8.29)	0.14

%: percent, ASDAS- CRP: Ankylosing Spondylitis Disease Activity Score with CRP, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BMD: bone mineral density, BMI: body mass index, CRP: C reactive protein, m: mean, mny: modified new York criteria, mSASSS: modified Stokes Ankylosing Spondylitis Spinal Score, n: number, NA: not applicable, NSAIDs score: non-steroidal anti-inflammatory drugs, SPARCC SIJ: SpondyloArthritis Research Consortium of Canada sacroiliac joint, SPARCC Spine: SpondyloArthritis Research Consortium of Canada spine, S.D: standard deviation, SMD: standardized mean difference, w weeks.