Benefits and risks of targeted treatment in rheumatoid arthritis

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2012

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CHAPTER 3.

Changes in hand bone mineral density are associated with the level of disease activity in patients with early rheumatoid arthritis: Bone mineral density measurements in the BeSt study

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Title: 'Changes in hand bone mineral density and the association with the level of disease activity in patients with rheumatoid arthritis: bone mineral density measurements in a multicenter randomized clinical trial'

Arthritis Care Res (Hoboken). 2011 Dec;63(12):1691-09

ABSTRACT

Objective

We hypothesized that, since bone is dynamic, if bone mineral density (BMD) loss in rheumatoid arthritis (RA) is driven by inflammation, patients in remission could show BMD gain.

Methods

Metacarpal BMD (mBMD) was measured by DXR in consecutive radiographs of 145 patients with RA with continuous high (HDA, DAS >2.4) or low (LDA, 1.6≥ DAS ≤2.4) disease activity and patients in continuous clinical remission (CR, DAS <1.6) during a 1 year observation period. Association of mBMD changes with disease activity was investigated with multinomial regression analysis. Next, clinical variables associated with mBMD gain were identified.

Results

Mean mBMD in CR patients was -0.03%, compared to -3.13% and -2.03% in HDA and LDA patients (overall, $p < 0.001$). Of the patients in CR, 32% had mBMD loss (≤-4.6 mg/cm^2/year), compared to 62% and 66% of the patients with HDA or LDA, whereas 26% of the patients in CR had mBMD gain (≥4.6 mg/cm^2/year), compared to 2% of the patients with HDA and 5% of the patients with LDA. Patients in CR had a higher chance of having mBMD gain, compared with LDA and HDA (RR 14.9, 95% CI: 3.0-18.7 and RR 4.7, 95% CI: 1.2-6.3, respectively). Clinical remission, hormone replacement therapy and a lower age were significant independent predictors of mBMD gain.

Conclusion

In recent onset RA, mBMD gain occurs primarily in patients in continuous (>=1 year) clinical remission and rarely in patients with continuous high or low disease activity. This suggests that mBMD loss is driven by inflammation.

INTRODUCTION

Bone damage in rheumatoid arthritis (RA) is present in erosions as well as in accelerated bone mineral density (BMD) loss at the spine and hips (generalized bone loss) and at the hand (local bone loss).(1;2) Hand BMD loss in RA is reported to precede radiographic joint damage.(3-5) It has been observed in very early stages of RA including in patients with undifferentiated arthritis who later progressed to RA.(6;7)

BMD loss in RA is primarily thought to be the effect of an increased osteoclast activity (8) and to a lesser extent the effect of impairment of bone formation by osteoblasts.(9) Osteoclast activity is mainly regulated by tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, IL-17 and receptor activator of nuclear factor kappa B ligand (RANKL).(10-12) Levels of these cytokines are high when disease activity is high (13-21) and thus might contribute to bone loss. Moreover, BMD shows more rapid decrease in active disease compared to inactive disease.(22;23) This implies that the extent of BMD loss might be different for patients with different levels of disease activity. Given the fact that bone is a dynamic tissue, the balance between osteoclast and osteoblast activity may be restored and BMD loss may be (re)gained when disease activity is sufficiently suppressed. In RA, this would mean that patients need to be in prolonged remission.

Therefore, the aim of this study was to investigate differences in hand BMD changes, measured with DXR at the metacarpals, over a period of one year between patients with high and low disease activity and patients in clinical remission during that period. It was hypothesized that inflammation drives BMD loss and that therefore patients in remission might show an increase in BMD.

PATIENTS AND METHODS

Patients

For the current analysis, all patients participating in the BeSt trial with either standard analogue radiographs of both hands or digital radiographs of both hands at two consecutive time points over 1 year follow-up, were selected. From these, patients with continuous (at all time points during that year of follow up) clinical remission (DAS <1.6), low disease activity (DAS>1.6 but =<2.4) or high disease activity (DAS>2.4) were selected. The result is a subpopulation of 145 of the original 508 patients participating in the BeSt trial. The disease activity score used in this study is the original DAS, with a 44 swollen and 53 tender joint count.

The BeSt trial is a multi-centre, randomized clinical trial comparing four different treatment strategies in DMARD-naïve patients who fulfilled the revised inclusion criteria for RA as defined by the American College of Rheumatology (ACR) in 1987. Patients were randomized to one of four treatment strategies: sequential monotherapy; step-up therapy; initial combination therapy with tapered high-dose of prednisone; or initial combination therapy including infliximab. Treatment adjustments were made every three months aiming at a disease activity score (DAS) ≤ 2.4. More details on the BeSt study design were previously published.(24-26)

Hand bone mineral density measurements

Digital X-ray radiogrammety (DXR) was used (27) to measure metacarpal BMD (mBMD). The analogue radiographs were first digitalized by a high-resolution 300 DPI scanner (Canon Vidar VXR-12 plus), before mBMD was measured. Mean surrogate mBMD was calculated from cortical thickness at the centre of metacarpals II, III and IV through an automated analysis of a standard projection digital radiograph of the hands using DXR online technology (Sectra, Sweden). Mean mBMD of both hands was used for the analysis in order to avoid bias of the dominant and non-dominant hands. mBMD loss was defined as a change in mBMD ≤ -4.6 mg/cm^2/year, mBMD gain was defined as a change in mBMD ≥ 4.6 mg/cm^2/year and a stable mBMD was defined as a change of -4.6 > mBMD < 4.6 mg/cm^2/year, according to the smallest detectable difference.(28)

Baseline and follow-up

As mentioned, patients were divided into three groups based on the level of continuous disease activity over the one year follow-up period: continuous high disease activity (DAS > 2.4), continuous low disease activity (1.6 ≤ DAS ≤ 2.4) and continuous clinical remission (DAS < 1.6). 'Baseline' in this analysis denotes the start of the one year follow up period in which mBMD was measured, not inclusion in the trial. Patients with continuous high disease activity were predominantly found in the first year after inclusion while patients in continuous clinical remission were particularly found in the third and fourth year after inclusion. As a result, some patients were treated with anti-rheumatic medication before the start of the follow up period ('baseline') and others were not. For each individual, all demographic and clinical variables were adjusted to their specific 'baseline' and 'follow-up' values.

Demographic and clinical variables

The following 'baseline' variables were collected in all patients: age, gender, body mass index (BMI), disease activity score (DAS), functional ability as measured by Health Assessment Questionnaire (HAQ), presence of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA), arthritic symptom duration, race, current smoking and alcohol status, postmenopausal status, osteoporosis in first-degree relatives, the use of bisphosphonates, calcium, vitamin D and hormone replacement therapy (HRT) and lastly current and previous use of anti-rheumatic medication.

Radiographic joint damage was assessed according to the Sharp-van der Heijde method.(29) Radiographs were scored in random order by two independent readers who were blinded for patient identity and treatment allocation. The interobserver correlation coefficient was 0.93 and the intraobserver coefficients were 0.93 and 0.94. The mean score from the readers was used for the analysis.

Statistical analysis

'Baseline' characteristics were compared between the three defined groups. Differences were tested using the chi-square test for categorical data and either one-way analysis of variance or Kruskal-Wallis test for continuous data, depending on the distribution of the

tested variable. In case of an overall significant difference, a post-hoc analysis was performed. A multinomial regression analysis was performed to identify variables showing an association with changes in metacarpal BMD. The variables entered were age, gender, BMI, symptom duration, DAS at baseline and it components SJC, RAI, VAS global health and ESR, RF and ACPA status, erosions at baseline, delta SHS, previous treatment, current treatment and antiresorptive therapy. Disease activity score was first entered as a continuous variable (AUC of the DAS) and next as a categorical variable (three predetermined groups). Variables showing an association with changes in mBMD were entered as possible predictors in a multivariate multinomial regression analysis. With a backward selection procedure, using a p-value of 0.10 as the removal criterion, associations with mBMD were identified. Several obtained odds ratios were corrected into relative risks with the formula of Zhang and Yu (30) in order to interpret the magnitude of the associations more appropriately.

Lastly, the association between mBMD and the SHS score was investigated in the three disease activity groups with a Kruskal-Wallis one way analysis of variance. The p-values derived in these tests were corrected for multiple comparisons by the step-down Bonferroni–Holmes adjustment. All tests were two-tailed and $p < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics, for each defined patient group, are shown in table 1. The selected patients (n=145) were on average 56 years old, most patients were female (68%) and postmenopausal (68%) and 50% and 54% of the patients were RF and ACPA positive, respectively. Erosive disease was present in 47% of the patients. These patients did not differ at baseline from the other patients in the BeSt cohort (n=363) regarding disease activity (and the components of the DAS), HAQ, BMI, age, gender, symptom duration, presence of erosions and smoking status. However, patients with BMD measurements were more often ACPA and RF negative.

Since the patients in each disease activity category were mostly found in different years of follow-up in the BeSt cohort, there were differences in previous as well as in current

antirheumatic treatment. Further, patients in continuous clinical remission were also older, more often male, and the women more often postmenopausal and more patients in continuous clinical remission reported use of alcohol than patients with a high or low disease activity. Use of calcium, vitamin D, bisphosphonates and HRT was similar in the three groups.

BMD change

Overall mean metacarpal BMD at 'baseline' was 0.58 ± 0.08 g/cm^2. After one year, mean absolute change in mBMD was -0.002 ± 0.01 g/cm^2 for patients in continuous clinical remission, -0.019 ± 0.01 g/cm^2 for patients with continuous low disease activity and -0.018 ± 0.02 g/cm^2 for patients with continuous high disease activity. These values correspond with a mBMD loss of -0.034%, -2.03% and -3.13% in patients in continuous clinical remission and with continuous low and continuous high disease activity, respectively (overall $p < 0.001$; patients in remission had less mBMD loss than patients with low or high disease activity). Accelerated mBMD loss, defined as mBMD loss over 4.6 mg/cm^2/year (28) was found in 32% of the patients in continuous clinical remission, 66% of the patients with continuous low and 62% of the patients with continuous high disease activity. mBMD gain was observed in 26% of the patients in continuous clinical remission, compared to 5% of the patients with continuous low and 2% of the patients with continuous high disease activity ($p < 0.001$; patients in remission had more often mBMD gain than patients with low or high disease activity). Percentages of patients with stable mBMD were similar in both groups (figure 1).

Association between BMD and disease activity

With univariate multinomial analysis, variables associated with changes in mBMD were identified (table 2). These were entered in the multivariate multinomial analysis together with other possible confounders. Previous and current use of prednisone or infliximab was not significantly associated with mBMD changes, nor was use of bisphosphonates, calcium and vitamin D. On the other hand, use of HRT was significantly associated.

In the multivariate multinomial analysis, with stable mBMD as reference, continuous disease activity, presented as the AUC of the DAS, showed an independent association

with mBMD gain. There was an independent association of higher disease activity with mBMD loss (OR 1.5, 95% CI: 1.1-2.0) and higher disease activity was inversely associated with mBMD gain (OR 0.2, 95% CI: 01-0.6). HRT was independently associated with mBMD gain (OR 17.1, 95% CI: 2.7-107.5). When components of the DAS were entered in the multivariate analysis instead of the complete DAS, none of the components was independently predictive of mBMD. Therefore, the DAS itself was chosen for further analysis.

An association between disease activity and mBMD change was identified and next it was investigated if there was a dose-response relationship. Therefore, categorized DAS, as used to define the three disease activity groups, was entered in the multinomial regression analysis together with possible confounders. Categorized DAS was independently associated with mBMD gain (table 3). Patients in continuous clinical remission had a significantly higher chance of mBMD gain compared to patients with a continuous high disease activity (RR 14.9, 95% CI: 3.0-18.7) and to patients with continuous low disease activity (RR 4.7, 95% CI: 1.2-6.3). Compared to patients with continuous high disease activity, patients with continuous low disease activity had a similar chance of having mBMD gain (RR 3.9, 95% CI: 0.3-15.1). Further, compared to patients with continuous high disease activity, mBMD loss was significantly less in patients in continuous clinical remission (RR 0.5, 95% CI: 0.3-0.9), but not in patients with continuous low disease activity (RR 1.0, 95% CI: 0.7-1.3).

With stable mBMD as reference, continuous clinical remission was significantly associated with mBMD gain (RR 14.9, 95% CI: 3.0-18.7; OR 211.5, 95% CI: 10.9-4097.5). With mBMD loss as reference, continuous clinical remission was again significantly predictive of mBMD gain when compared to HDA (RR 27.9, 95% CI: 8.3-31.8; OR 64.5, 95% CI: 3.4-1228.9). HRT (RR 9.3, 95% CI: 1.2-25.9; OR 12.8, 95% CI: 1.2-132.5) and lower age (OR 0.95, 95% CI: 0.91-0.998) were also independent predictors for mBMD gain.

Association between BMD and radiographic damage

The mean (median (IQR)) change in SHS in the year of follow-up was 0.02 ± 0.7 (0 (0-0.13)) for patients with mBMD gain, 1.2 ± 4.2 (0 (0-0.9)) for patients with stable mBMD

and 4.4 ± 19.7 (0.3 (0-2)) for patients with mBMD loss (overall p = 0.056) (figure 2). Few patients had rapid radiological progression: 8% showed progression of ≥ 5 SHS points, 20% showed progression ≥ 2 points and 38% of the patients showed radiographic progression of ≥ 0.5 point. Of the patients with mBMD gain, 22% showed radiographic progression of ≥ 0.5 point, 6% progressed ≥ 2 points and none showed radiographic progression ≥ 5 points, whereas of the patients with mBMD loss, 50% had radiographic progression of ≥ 0.5 point, 30% progressed ≥ 2 points and 11% ≥ 5 points. Patients with mBMD gain had significant less often progression of ≥ 0.5 and 2 points than patients with mBMD loss (both $p < 0.05$), but no difference was found regarding progression ≥ 5 points ($p = 0.135$).

DISCUSSION

In patients with RA treated according to a protocol aimed at achieving and maintaining low disease activity (DAS=<2.4), we have shown that a gain in metacarpal BMD can occur, predominantly in patients who are in prolonged clinical remission. An increase in mBMD was rare in patients with continuous high disease activity (DAS>2.4) but also rare in patients with continuous low disease activity (DAS=<2.4 but >1.6). These results are encouraging as they indicate that bone damage in RA can be a reversible process.

In previous RA cohorts, generalized as well as metacarpal BMD loss, but not BMD gain, has been frequently observed.(4;5;7;23;31-35) Considering findings that osteoclast and osteoblast activity are influenced by inflammatory cytokines and vary with disease activity(10-21), we hypothesized that inflammation drives mBMD loss and that due to the dynamics of bone metabolism, patients who are in remission might show an increase in their mBMD. Our findings support this hypothesis. Previously, no difference in generalized BMD loss, measured by DEXA, was found between patients in remission or patients with high disease activity.(36) In the BeSt study, we have shown that changes in mBMD may be more sensitive to differences in inflammatory activity than changes in generalized BMD.(33;34)

Besides continuous clinical remission, age and HRT were also independent predictors of mBMD gain. Patients with higher age were unlikely to show mBMD gain, which may be

due to hormonal changes in this predominantly female population. HRT probably may have a positive effect on bone metabolism directly through actions on osteoclasts and osteoblasts as well as indirectly through effects on inflammatory cells and processes.(37) The use of bisphosphonates, calcium and vitamin D was not predictive of mBMD changes. Previously, we showed that bisphosphanates have a protective effect on generalized but not metacarpal BMD loss.(34)

In this cohort, any DAS>2.4 is considered to represent high (not moderate) disease activity, requiring adjustment of treatment. DAS=<2.4 but >1.6 was considered low. Continuously low disease activity did not appear to have many advantages for mBMD outcomes compared to continuously high disease activity. Although this first report on mBMD gain in patients in remission is encouraging, still only 26% showed mBMD gain. Possibly, factors such as lack of weight bearing exercise, dietary or endocrinological imbalances caused ongoing mBMD loss. It may also be that the remission definition of DAS <1.6 is insufficiently strict to identify true clinical remission, or residual inflammation remained undetected by clinical evaluation. Signs of synovitis can still be detected with magnetic resonance imaging in patients in clinical remission (38;39) and progression of joint damage has been reported in patients in clinical remission.(40;41) In that case metacarpal BMD loss may be a signal of ongoing disease activity, and mBMD measurement may help to identify patients at risk for radiographic progression who clinically appear to be in remission. Previous studies showed that mBMD loss precedes radiographic progression (6;7) and subsequently functional disability.(42;43) We found that patients with mBMD gain suffer hardly any radiographic progression, while patients with stable mBMD or mBMD loss did suffer radiographic progression more often. However, differences between the three groups were not significant because progression rates were low and few patients showed significant progression, since treatment in this cohort was aimed at achieving a DAS =<2.4.

This study has some limitations. Since in this cohort high disease activity occurred primarily early in the treatment period and sustained remission relatively late, there are differences in antirheumatic medication used in the year of observation in the three groups (table1). Prednisone has shown to have a deleterious effect on bone (44-46), while of infliximab a positive effect on BMD has been reported.(47;48) Our results showed no

association between previous and current use of prednisone and infliximab and mBMD and no differences in percentages of mBMD loss, mBMD gain or stable mBMD were found between patients in remission while on medication and patients in drug-free remission (data not shown). Thus, it seems unlikely that mBMD gain or loss are primarily drug effects. Also, the results show wide confidence intervals, indicating that they are not very accurate. This might be due to some small patient numbers in the different groups: hardly any patients in low and high disease activity group showed mBMD gain (figure 1). A larger cohort might reproduce more accurate results. Lastly, measuring mBMD with DXR always results in some measurement error.(28) This error would, however, be nondifferential and resulting in a bias similar for all disease activity groups.

In conclusion, in patients with rheumatoid arthritis, an increase in metacarpal BMD can occur, primarily in patients in continuous clinical remission (DAS <1.6) and rarely in patients with a continuous high (DAS >2.4) or low (DAS =<2.4 but >=1.6) disease activity. These findings suggest a link between inflammatory activity and metacarpal BMD loss. This puts a different perspective on RA, which is generally considered to be a chronic progressive disease, rather than a reversible disorder, and it points towards remission as the optimal treatment goal in patients with rheumatoid arthritis.

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Table 1. Baseline (i.e. start of 1 year follow up) characteristics of the three different disease activity groups.

Variables	Continuous clinical remission (DAS<1.6) n=57	Continuous low disease activity (1.6≤DAS≥2.4) n=38	Continuous high disease activity (DAS>2.4) n=50	P-value
Demographic				
Women, no. (%)	29 (51)	29 (76)	40 (80)	0.002
Postmenopausal status, no. (%)	22 (76)	16 (55)	27 (73)	0.002
Age, years, mean (SD)	60 (14)	53 (15)	53 (15)	0.014
BMI, kg/m^2, mean (SD)	25.7 (3.0)	26.0 (2.8)	26.8 (4.8)	0.305
Caucasian race, no. (%)	55 (97)	34 (90)	47 (94)	0.380
Current smoker, no. (%)	13 (23)	12 (32)	21 (42)	0.080
Current alcohol use, no. (%)	33 (58)	15 (40)	10 (20)	0.000
Familial osteoporosis, no. (%)	11 (20)	6 (16)	11 (22)	0.738
RA activity				
Symptom duration, years, median (IQR)	3.0 (1.5-3.5)	1.6 (1.3-2.4)	0.6 (0.3-1.1)	0.000
Time from inclusion in trial, mean (SD)	2.0 (1.1)	1.2 (0.5)	0.1 (0.3)	0.000
ACPA, no. (%)	24 (42)	19 (50)	29 (58)	0.260
RF, no. (%)	29 (51)	19 (50)	30 (60)	0.552
DAS, median (IQR)	0.9 (0.6-1.2)	2.1 (1.7-2.4)	4.6 (4.1-5.1)	0.000
HAQ, median (IQR)	0.0 (0.0-0.3)	0.4 (0.1-0.6)	1.4 (1.0-2.0)	0.000
Total SHS, median (IQR)	3.0 (0.5-7.8)	2.0 (0.3-12.0)	2.5 (0.0-5.4)	0.414
Mean (SD)	6.5 (9.0)	7.2 (9.6)	4.9 (9.6)	
SHS JSN score, median (IQR)	1.5 (0.0-5.0)	1.0 (0.0-4.5)	0.3 (0.0-2.9)	0.317
Mean (SD)	3.5 (4.8)	3.4 (5.3)	2.8 (6.6)	
SHS erosion score, median (IQR)	0.5 (0.0-2.8)	1.0 (0.0-6.5)	0.5 (0.0-2.5)	0.432
Mean (SD)	3.0 (5.3)	3.8 (5.2)	2.1 (3.5)	
Erosive disease, no. (%)	24 (42)	21 (57)	23 (47)	0.379
Metacarpal BMD, g/cm^2, mean (SD)	0.59 (0.09)	0.57 (0.08)	0.58 (0.07)	0.488
RA and osteoporotic treatment in the year of follow-up				
RA treatment groups, no. (%)				
Sequential monotherapy	14 (25)	3 (8)	16 (32)	
Step up from mono to combo therapy	9 (16)	11 (29)	14 (28)	0.079
Initial combo therapy with prednisone	15 (26)	12 (32)	11 (22)	
Initial combo therapy with infliximab	19 (33)	12 (32)	9 (18)	
RA treatment history, (%)				
No treatment	0	0	90	0.000
MTX	40	11	2	0.000
SSA	7	8	0	0.142
Other DMARDs	2	3	4	0.777

Combo therapy (MTX, SSA, pred)	26	32	8	0.014
Other DMARD combo therapy	2	32	6	0.000
Combo therapy IFX + MTX	33	32	4	0.000
RA active treatment, no. (%)				
No treatment	26 (46)	0 (0)	0 (0)	0.000
MTX monotherapy	10 (18)	6 (16)	29 (58)	0.000
Other DMARD monotherapy	2 (4)	3 (8)	1 (2)	0.371
Combo therapy (MTX, SSA, pred)	10 (18)	12 (32)	9 (18)	0.203
Other DMARD combo therapy	0 (0)	7 (18)	1 (2)	0.000
Combo therapy IFX + MTX	9 (16)	10 (26)	10 (20)	0.454
Osteoporotic treatment, no. (%)				
Bisphosphonates	10 (18)	5 (13)	7 (14)	0.779
Calcium supplements	17 (30)	11 (29)	12 (24)	0.779
Vitamin D Supplements	6 (11)	6 (16)	5 (10)	0.661
HRT	5 (9)	6 (16)	10 (20)	0.266

DAS, disease activity score; SD, standard deviation; BMI, body mass index; IQR, inter quartile range; ACPA, anti-cyclic citrullinated peptide antibodies; RF, rheumatoid factor; HAQ, Health Assessment Questionnaire; SHS, Sharp van der Heijde Score; JSN, joint space narrowing; BMD, bone mineral density; RA, rheumatoid arthritis; MTX, methotrexate; DMARD, SSA, sulphasalazine; disease-modifying antirheumatic drug; pred, prednisone; IFX, infliximab; HRT, hormone replacement therapy.

Table 2. Univariate predictive variables of an increase or loss in mBMD compared to a stable mBMD presented in odds ratios (OR) and their 95% CI.

Variable OR (95% CI)	mBMD increase n=18	mBMD loss n = 74
Age, years	0.98 (0.95-1.02)	1.01 (0.99-1.04)
Female gender	1.6 (0.5-5.1)	1.4 (0.7- 3.0)
BMI, kg/m^2	0.8 (0.7-0.99)*	0.97 (0.9-1.1)
DAS baseline	0.5 (0.3-0.9)*	1.3 (1.03-1.6)*
AUC DAS	0.3 (0.2-0.7)*	1.4 (1.1-1.9)*
SJC baseline	0.9 (0.8-1.03)*	1.1 (1.0-1.1)
ESR baseline	0.96 (0.93-1.01)	1.01 (1.00-1.03)
RAI baseline	0.8 (0.7-0.99)*	1.03 (0.99-1.08)
VAS global health baseline	0.95 (0.91-0.99)*	1.01 (1.00-1.03)*
Symptom duration	1.2 (0.9-1.5)	0.8 (0.6-1.1)
Erosive at baseline	0.5 (0.2-1.6)	1.04 (0.5-2.1)
Δ SHS	0.7 (0.5-1.1)	1.04 (0.96-1.1)
BMD baseline	7.0 (0.01-5924.6)	0.2 (0.00-8.9)
RF positive	1.3 (0.4-3.8)	0.7 (0.4-1.5)
ACPA positive	0.5 (0.1-1.5)	1.7 (0.8-34)
Vitamin D and/or Calcium	0.7 (0.2-2.3)	1.2 (0.6-2.5)
HRT	4.8 (1.3-18.4)*	1.5 (0.5-4.8)
Bisphosphonate use	0.8 (0.2-4.4)	1.4 (0.5-3.8)

BMI, body mass index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; RAI, Ritchie Articular Index; VAS global health, visual analogue scale global health; SHS, Sharp van der Heijde score; BMD, bone mineral density; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies; HRT, hormone replacement therapy. Stable BMD is used as reference category. * $p < 0.05$.

Table 3. Associations between disease activity and mBMD, with stable mBMD and HDA as reference category, presented in relative risks (RR) and their 95% CI

		mBMD gain ($\geq$0.0046 g/cm^2)	mBMD loss ($\leq$ -0.0046 gm/cm^2)
Remission (DAS < 1.6)	RR	14.9 (3.0-18.7)	0.3 (0.1-0.8)
LDA (1.6 $\leq$ DAS $\leq$ 2.4)	RR	3.9 (0.3-15.1)	1.1 (0.5-1.7)

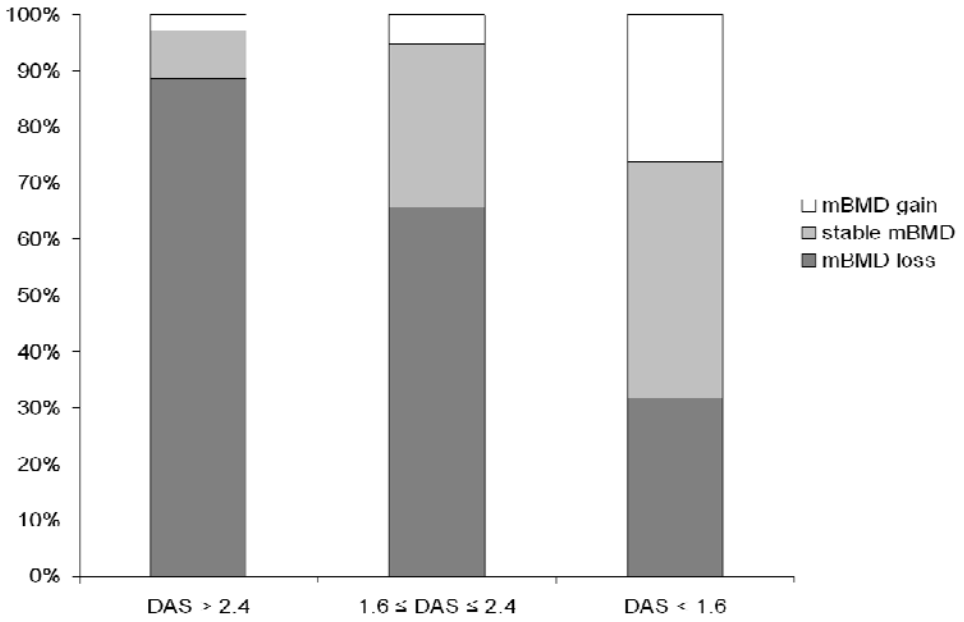

Figure 1. Dynamics of mBMD in patients with (1) continuous high disease activity (DAS > 2.4), (2) continuous moderate disease activity (1.6 ≤ DAS ≤ 2.4) and (3) continuous clinical remission (DAS < 1.6), during 1 year follow-up.

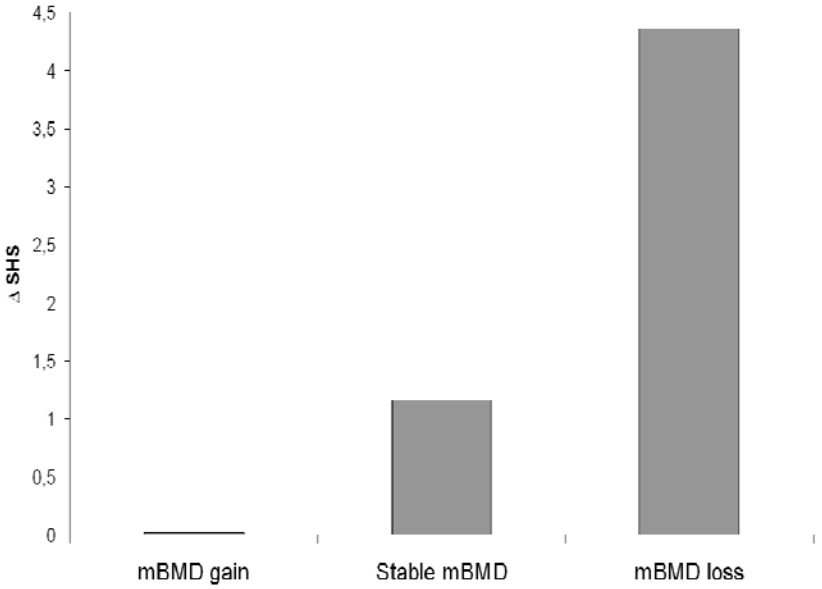

Figure 2. Mean changes in SHS score in patients having (1) mBMD gain, (2) stable mBMD or (3) mBMD loss, during 1 year follow-up.