

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/medici>

Original Research Article

Factors associated with bone mineral density loss in patients with spondyloarthropathies: A 4-year follow-up study

Lina Vencevičienė^{a,*}, Irena Butrimienė^{b,c}, Rimantas Vencevičius^d, Eglė Sadauskienė^e, Vytautas Kasiulevičius^a, Virginijus Šapoka^f

^a Centre of Family Medicine, Vilnius University, Vilnius, Lithuania

^b Centre of Rheumatology, Vilnius University, Vilnius, Lithuania

^c Centre for Innovative Medicine, State Research Institute, Vilnius, Lithuania

^d Centre of Traumatology, Orthopedics and Plastic and Reconstructive Surgery, Vilnius University, Vilnius, Lithuania

^e Centre of Cardiology and Angiology, Vilnius University, Vilnius, Lithuania

^f Centre of Internal Medicine, Vilnius University, Vilnius, Lithuania

ARTICLE INFO

Article history:

Received 11 December 2014

Received in revised form

28 July 2015

Accepted 9 August 2015

Available online 9 September 2015

Keywords:

Spondyloarthropathies

Bone mineral density

Anti-TNF α

ABSTRACT

Objective: To explore the relationship between laboratory, functional, disease activity markers and bone mineral density (BMD) loss in patients with spondyloarthropathies (SpAs).

Methods: A cohort of 41 SpA patients were followed up for 4 years. Disease activity indices, spinal mobility and laboratory tests, BMD using were monitored at the baseline and 4-year follow-up. The 4% BMD loss at either of the proximal femurs was defined as significant.

Results: Over the 4-year study period, 27% of SpA patients experienced femoral BMD loss. Baseline BMD $> 0.85 \text{ g/cm}^2$ ($p = 0.011$) was the baseline factor associated with BMD loss at 4-year follow-up. Several clinical and functional tests were helpful in identifying the BMD loss at follow-up: CRP $> 15.6 \text{ mg/L}$ (sens. 91%, spec. 70%), ESR $> 29 \text{ mm/h}$ (sens. 82%, spec. 73%), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) > 4.75 (sens. 91%, spec. 62%). At follow-up anti-TNF α treatment history, stable or improved lateral flexion and intermalleolar distance (NPV, accordingly, 95%, 88% and 87%), made BMD loss unlikely. Deterioration of the physician assessment of global disease activity (PAGDA) score from baseline to follow-up was a remarkable predictor of BMD loss (PPV = 0.83), while stable or improved score excluded the BMD loss (NPV = 0.83). According to multiple logistic regression analysis, baseline BMD value and follow-up CRP levels, when considered together, identify BMD status correctly in 85% of SpA patients (Nagelkerke $R^2 = 0.676$).

* Corresponding author at: Centre of Family Medicine, Vilnius University Hospital Santariškių Klinikos, Santariškių 2, LT-08661 Vilnius, Lithuania. Tel.: +370 61278840; fax: +370 52365034.

E-mail address: linaven@gmail.com (L. Vencevičienė).

Peer review under the responsibility of the Lithuanian University of the Health Sciences.



Production and hosting by Elsevier

<http://dx.doi.org/10.1016/j.medici.2015.08.001>

1010-660X/© 2015 Lithuanian University of Health Sciences. Production and hosting by Elsevier Sp. z o.o. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Conclusion: Baseline BMD, anti-TNF α treatment, PAGDA score, spinal mobility tests and disease activity markers are useful factors in predicting the BMD loss in SpA patients and can provide surrogate information on BMD status.

© 2015 Lithuanian University of Health Sciences. Production and hosting by Elsevier Sp. z o.o. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Spondyloarthropathies (SpA) include a group of chronic inflammatory diseases, of which the main ones are ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) and enteropathic arthropathies (EnA). These disorders share several clinical features, such as inflammation of the axial joints and skeleton, asymmetric oligoarthritis and enthesitis. Syndesmophyte formation and bone erosions are hallmarks of SpA skeletal complications. However, while accounting for a significant proportion of SpA-related disability, the loss of bone mineral density (BMD) is commonly ignored [1,2]. The reported prevalence of BMD loss among SpA patients varies between 19% and 62%, while its onset during the first decade of the disease is common [3,4]. In overall, SpA patients demonstrate a significantly lower proximal femur and lumbar BMD than the control group and BMD loss becomes more prominent with the increasing length of the disease [5,6]. The resultant osteopenia or osteoporosis often leads to pathological fractures, limiting the quality of life in SpA patients [3,6–8]. Therefore the early identification and management of the SpA patients who are at risk of BMD loss could offer a treatment advantage.

A dual energy X-ray absorptiometry (DXA) scan is a gold standard for BMD assessment [9]. However, regular DXA scan-based SpA patient screening for BMD loss remains a contentious subject. Lateral lumbar and femoral DXA scans have been shown to be superior to traditional PA lumbar DXA scan, which is susceptible to syndesmophyte interference [6]. Yet lateral and femoral DXA measurements have not been validated for BMD measurement in SpA patients outside the research setting. Secondly, many SpA patients do not undergo BMD loss and can have stable BMD for decades [10]. Therefore, routine DXA scans are unnecessary for certain SpA patient populations and, in this way, provide an opportunity to reduce health care expenditures. Since DXA scanners are not available in many resource-restricted hospitals, cheap and accurate surrogate markers of BMD loss would allow for better SpA patient care in these settings.

Previously the challenge to identify SpA factors associated with BMD loss has been predominantly addressed by cross-sectional studies [8,11–14]. In addition, several longitudinal studies have investigated the relationship between BMD and bone turnover factors [15,16]. However, to the best of our knowledge, this is one of the few longitudinal studies evaluating the relationship between routine laboratory tests, disease activity indices and spinal mobility tests and BMD loss in SpA patients. We followed up SpA patients for 4 years to identify the surrogate markers of the

BMD loss and baseline factors associated with BMD loss at follow-up.

2. Methods

2.1. Study population and subject selection

The study enrolled 41 SpA patients from the Centre of Rheumatology, Vilnius University, who were seen between 2008 and 2012. The inclusion criteria were age (between 20 and 75 years) and fulfilment of the European Spondyloarthropathy Study Group criteria for the classification of SpA [17]. Patients with kidney, liver, thyroid, parathyroid, oncological or other diseases, which can affect calcium and bone metabolism, were excluded. Other exclusion criteria were pregnancy, being a vegetarian, alcohol abuse, taking anticonvulsants, insulin, thyroxine, anticoagulants, hormonal replacement therapy, vitamin D supplements, bisphosphonates and other compounds that interfere with bone metabolism [18]. Patients taking disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs, corticosteroids, disease modifying drugs, such as sulphasalazine, methotrexate or tumor necrosis factor α inhibitors (anti-TNF α) were included.

2.2. Ethics and consent

All study participants signed an informed consent form approved by the Lithuanian Bioethics Committee (N $^{\circ}$ 60, 2006-12-22).

2.3. Data collection

At baseline and follow-up visits all patients provided a complete medical history and underwent clinical examination by a rheumatologist. Anthropometric and spinal mobility measurements were recorded. Disease activity scores, laboratory investigations and a DXA scan were also performed during both visits. Clinical assessment included collection of demographic and clinical data (age, gender, age of menarche and menopause for women, smoking and alcohol consumption, history of bone fractures, co-existing diseases, medications and dietary supplements, pain [VAS score] and general health assessment). The type of spondyloarthropathy was determined using the European Spondyloarthropathy Study Group criteria for the classification of SpA [17]. Medical records were reviewed to find evidence of previous or current treatment with anti-TNF α and to quantify the duration and cumulative dose of glucocorticoid (GC) treatment.

The body mass index (BMI) (kg/m^2) and performance in spinal mobility tests, including lumbar side flexion [19], modified Schober's test [20], tragus to wall distance and intermalleolar distance [21,22] were obtained for every patient. The best result of two attempts for each functional test was recorded. Disease activity was evaluated by physician's assessment of global disease activity (PAGDA) score (1 – inactive disease, 2 – low activity, 3 – moderate activity, 4 – high activity) [23]. In addition, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (0–10) [24], Bath Ankylosing Spondylitis Functional Index (BASFI) (0–10) [25] and Health Assessment Questionnaire Modified for Spondyloarthropathies (HAQ-S) (0–3) [26] scores were collected. All patients were examined by the same researcher (L.V.).

2.4. DXA scans

BMD of both proximal femurs was measured at baseline and after 4 years using the dual-energy X-ray absorptiometry (Lexus – DMS osteodensitometer®, France) and was expressed as total femoral BMD (g/cm^2). While the anterior–posterior lumbar DXA test has adequate sensitivity for assessing the BMD changes in early SpA, the scan gives paradoxically high BMD values in the setting of more severe disease when syndesmophyte formation, ligament and vertebral disc calcifications occur [5,6,27]. In this study we measured the BMD of proximal femur as these BMD values were shown to correlate with the risk of vertebral fractures, but are not influenced by syndesmophyte formation [28]. As we previously demonstrated that lumbar spine and proximal femur BMD changes are similar across all types of spondyloarthropathies, the same BMD assessment was valid for AS, PsA, EnA and ReA patients [5].

The short-term precision for proximal femur BMD measurements had a coefficient of variation (CV) of 1.4% (assessment performed by the researcher L.V.). The least significant change (LSC) in BMD, which can be recognized with 95% confidence, is calculated: $2.77 \times \text{CV}$ [29]. If the measured BMD change equals or exceeds the LSC, one is reasonably confident that the true bone loss or gain in the patients has actually occurred. Using our DXA scanner the LSC in proximal femur BMD was $2.77 \times 1.4\% = 3.88\%$. Therefore a significant decrease in BMD was defined as a 4% BMD decrease in either of the proximal femurs.

2.5. Statistical analysis

Statistical analysis was carried out using the SPSS v17.0 (IBM, Armonk, NY, USA) software. Data were presented as mean $\pm$ SD or as number (%), unless specified otherwise. Normality of variables was measured using Shapiro–Wilk test, skewness and kurtosis. It was assumed that both baseline and follow-up distributions of VAS score, BASDAI, BASFI, ESR and CRP were not normal, thus comparison between groups for these variables was conducted using Mann–Whitney *U* test. Other variables were compared using a Student *t*-test, while paired *t*-test was used for comparing the follow-up and baseline BMD data. 2×2 contingency tables were designed for categorical variables and all non-parametric data was analyzed using Fisher exact test. Multiple binary logistic regression analysis

(forward Wald) was used to assess, which baseline factors are independently associated with BMD loss. To estimate the cut-off values, sensitivity and specificity of surrogate markers of BMD loss, empirical ROC curve analysis was performed (95% CI). The level of significance was set at $p < 0.05$.

The BMD dynamics were measured in 2008 and repeatedly in 2012 in 41 patients (83% males) who met the inclusion criteria. More than half (51%) of patients had AS, 27% had PsA, 10% had EnA and 12% had ReA. At baseline the average age of all participants was 40.9 ± 10.5 years, while the average duration of the disease since diagnosis was 62.2 ± 63.5 months.

Over the 48 months 11 (27%) patients had BMD loss in either of the femurs. The prevalence of males in BMD loss and stable/increased BMD groups was not significantly different (73% vs 87%, $p = 0.27$). The age of patients with BMD loss and stable/increased BMD was similar at baseline (41.27 ± 10.45 vs 40.73 ± 10.72 months, $p = 0.89$) as was the time since the diagnosis of SpA (59.00 ± 65.34 vs 63.43 ± 63.88 months, $p = 0.28$). Generally, in all patients ($N = 41$) BMD did not change significantly over the 4 years: baseline left femur BMD vs follow-up BMD (0.842 vs 0.851 g/cm^2 , $p = 0.50$), right femur BMD (0.840 vs 0.858 g/cm^2 , $p = 0.10$). Since both left and right femur BMD results were nearly identical throughout the study, we used only left femur values for further analysis.

The SpA patients with either deteriorated or increased/stable BMD were compared in terms of baseline and follow-up demographic and clinical data (Table 1). Since only the decrease of BMD is a worrying feature in SpA patients, patients with either increased or stable BMD were grouped together ($N = 30$). None of the baseline variables that could affect BMD, such as disease duration, gender, patient age, BMI or inflammatory markers were statistically different between those two groups. In addition, there were no differences between different SpA types according BMD loss ($p = 0.101$). None of the disease activity and severity markers, such as BASDAI, BASFI, HAQ-S or visual analogue scale (VAS) pain rating, were different between the above-mentioned groups at the baseline.

At 4 year follow-up SpA patients with BMD loss demonstrated worse average BASDAI score than SpA patients with stable/raised BMD (6.28 vs 4.71 , $p = 0.016$). BMD loss was also associated with significantly raised inflammatory marker readings: ESR (36.82 vs 21.52 , $p = 0.010$) and CRP (32.90 vs 10.01 , $p = 0.003$). It is interesting to note that patients who underwent BMD loss during the 4-year period had a significantly higher baseline BMD than the stable group ($p < 0.001$) and exhibited a similar proximal femur BMD at 4-year follow-up.

There were no differences between the two groups in the duration and cumulative dose of GC treatment at both time points. At recruitment only 22% (9/41) of the whole cohort had been treated with anti-TNF α , while, by follow-up, 46% (19/41) had received this therapy. None of the 9 patients with a history of anti-TNF α treatment at baseline lost BMD over the next 4 years. At follow-up, 18/19 (94.7%) patients who received anti-TNF α therapy had stable or increased BMD (the mean anti-TNF α treatment duration was 72.7 ± 11.3 months). However, 10 patients from 22 not treated with anti-TNF α , lost BMD. The BMD loss rate of these patients was significantly higher than in the group treated with anti-TNF α (45.5% vs 5.3%; $p = 0.004$).

Table 1 – Clinical variables of patients with BMD loss and stable/increased BMD at baseline and 48 month follow-up.

	Baseline				48 months			
	Total (N = 41)	BMD loss (N = 11)	BMD increased/stable (N = 30)	p-Value	Total (N = 41)	BMD loss (N = 11)	BMD increased/stable (N = 30)	p-Value
Left femur BMD (g/cm ²)	0.842 ± 0.13	0.957 ± 0.08	0.799 ± 0.12	<0.001	0.851 ± 0.12	0.886 ± 0.08	0.837 ± 0.13	0.257
Right femur BMD (g/cm ²)	0.840 ± 0.12	0.938 ± 0.08	0.803 ± 0.11	0.001	0.858 ± 0.12	0.886 ± 0.07	0.847 ± 0.13	0.228
BMI (kg/m ²)	25.44 ± 4.94	25.56 ± 4.07	25.40 ± 5.29	0.915	26.98 ± 4.88	27.01 ± 4.90	26.98 ± 4.95	0.986
Pain VAS (0–100)	54.73 ± 20.37	53.00 ± 22.63	55.36 ± 19.90	0.660	42.20 ± 19.04	45.45 ± 18.09	41.00 ± 19.54	0.441
BASDAI (0–10)	4.43 ± 2.14	4.39 ± 2.07	4.44 ± 2.20	0.988	4.71 ± 2.50	6.28 ± 1.85	4.13 ± 2.48	0.016
HAQ-S (0–3)	0.78 ± 0.66	0.58 ± 0.62	0.85 ± 0.67	0.240	0.73 ± 0.64	1.00 ± 0.58	0.64 ± 0.64	0.101
BASFI (0–10)	4.04 ± 2.83	3.82 ± 2.64	4.12 ± 2.93	0.805	3.81 ± 4.42	4.75 ± 2.18	3.46 ± 2.44	0.085
ESR (mm/h)	37.64 ± 25.60	39.12 ± 32.36	37.10 ± 23.28	0.942	25.62 ± 16.64	36.82 ± 16.52	21.52 ± 14.93	0.010
CRP (mg/L)	23.79 ± 19.72	27.29 ± 25.33	22.51 ± 17.58	0.612	16.15 ± 18.37	32.90 ± 26.78	10.01 ± 8.52	0.003
TNF α blockers								
Treated	9 (22.0%)	0	9	0.041	19 (46.3%)	1	18	0.004
Not treated	32 (78.0%)	11	21		23 (53.7%)	10	12	

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMD, Bone mineral density; GC, glucocorticoids; HAQ-S, Health Assessment Questionnaire for the Spondylarthropathies; SpA – spondyloarthropathy; VAS –, spondyloarthropathy; VAS, Visual Analogue Scale. p-Values in bold are statistically significant.

Table 2 – The association between spine mobility test and physician assessment of global disease activity score change with BMD loss (N = 41).

	BMD loss	BMD stable/improved	Odds ratio [95% CI]	p
Tragus to wall distance				
Deteriorated	6	10	2.40 [0.59, 9.82]	0.223
Stable/improved	5	20		
Modified Schober test				
Deteriorated	8	12	4.00 [0.88, 18.19]	0.073
Stable/improved	3	18		
Lateral flexion				
Deteriorated	8	9	6.22 [1.33, 29.01]	0.020
Stable/improved	3	21		
Intermalleolar distance				
Deteriorated	8	10	5.33 [1.16, 24.60]	0.032
Stable/improved	3	20		
PAGDA score				
Deteriorated	5	1	24.17 [2.38, 245.92]	0.007
Stable/improved	6	29		

PAGDA, physician assessment for global disease activity. p-Values in bold are statistically significant.

Nineteen patients with positive anti-TNF α treatment status had, on average, 5.6% higher BMD at 4-year follow-up than at the baseline.

Similar results in spinal mobility tests were observed in both groups at baseline and follow-up. While most of the patients maintained stable spinal mobility readings, some had improved

or deteriorated results at 4-year follow-up. The deterioration in lateral flexion and intermalleolar distance readings over the 4-year period was associated with BMD loss (Table 2). On the other hand, patients with stable or improved intermalleolar distance (NPV = 0.87) or lateral flexion (NPV = 0.88) were unlikely to have decreased BMD (Table 3). Deterioration of the PAGDA

Table 3 – Performance of spinal mobility tests or PAGDA score in diagnosing the BMD loss at follow-up (N = 41).

	Sens. [%, 95% CI]	Spec. [%, 95% CI]	PPV [%, 95% CI]	NPV [%, 95% CI]
Deteriorated tragus to wall distance	54.6 [23.4–83.3]	66.7 [47.2–82.7]	37.5 [15.2–64.6]	80.0 [59.3–93.2]
Deteriorated modified Schober test score	72.7 [39.0–94.0]	60.0 [40.6–77.3]	40.0 [19.1–64.0]	85.7 [63.7–97.0]
Deteriorated lateral flexion	72.7 [39.0–94.0]	70.0 [50.6–85.3]	47.0 [23.0–72.2]	87.5 [67.6–97.3]
Deteriorated intermalleolar distance	72.7 [39.0–94.0]	66.7 [47.2–82.7]	44.4 [21.5–69.2]	87.0 [66.4–97.2]
Deteriorated PAGDA score	45.4 [16.8–76.6]	96.7 [82.8–99.9]	83.3 [35.9–99.6]	82.9 [66.4–93.4]

PAGDA, physician assessment for global disease activity; Sens., Sensitivity; Spec., specificity.

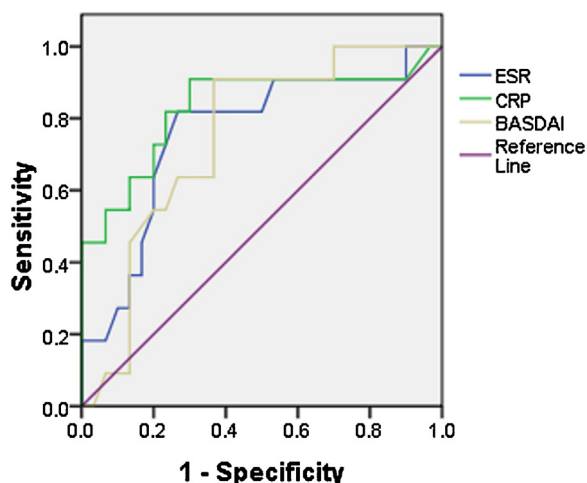


Figure – ROC curves of follow-up variables associated with BMD loss (N = 41).

score from baseline to follow-up was a remarkable predictor of BMD loss (PPV = 0.83), while a stable or improved score excluded the BMD loss equally well (NPV = 0.83).

Empirical ROC curves were constructed for significantly different continuous variables, measured at baseline and 4-year follow-up. ROC curves demonstrated that baseline left femur BMD > 0.8465 g/cm² foresees BMD loss in 4 years with 100% sensitivity and 76.7% specificity (AUC = 0.873). Among the follow-up continuous variables the biggest area under the curve (AUC) was observed in the CRP test (AUC = 0.830) and it was significantly higher than in ESR or BASDAI (Figure, Table 4).

At follow-up CRP and ESR readings above the cut-off values determined by ROC curves could pick out around 90% of patients with BMD loss (Table 4). Variables that had a statistically significant association with BMD loss were entered into a logistic regression analysis (forward Wald). Increased/stable BMD and BMD loss ($>4\%$ proximal femur BMD decrease) were set as a binary outcome. The analysis revealed that follow-up CRP ($\beta = 0.14$, $p = 0.025$) and initial proximal femur BMD ($\beta = 13.88$, $p = 0.011$) were two factors independently associated with BMD loss. In combination the knowledge of CRP levels at follow-up and initial proximal femur BMD allowed correct patient assignment into BMD loss or stable/improved BMD groups with 85.4% accuracy (Nagelkerke $R^2 = 0.676$).

3. Discussion

At present there is little evidence to support regular SpA patient screening for BMD loss [3]. It seems that costly routine DXA scanning of SpA patients would only benefit a small proportion of them. On the other hand, failing to identify BMD loss results in pathological fractures that often lead to significant morbidity. Therefore, indicators of probable BMD loss in SpA patients are needed by clinicians to build an optimal patient surveillance strategy. Our study analyzed the value of disease activity, functional and laboratory tests as surrogate markers of the BMD loss in SpA patients. We found that anti-TNF α treatment status, baseline BMD value, results of the spine mobility tests, PAGDA score and standard inflammatory markers can provide surrogate information about the BMD status during the follow-up visit.

BMD loss is a well-described feature in SpA patients [2,30]. Both disease duration and patient's age contribute to bone density changes. A recent systematic review reported a femoral BMD loss in 51% of AS patients within the first 10 years of diagnosis [4]. However, in our previous study, we demonstrated that the time of onset of clinical symptoms was a better predictor of BMD change rather than the time when the SpA diagnosis was given. Taking into account the effect of syndesmophyte formation on lumbar DXA readings, we concluded that with increasing disease duration upper femur BMD decreases, while spinal BMD increases [5].

In our current study 27% of SpA patients underwent a significant BMD deterioration during the 4-year period, on average losing 7.4% of their proximal femur BMD. Interestingly, the remaining 73% of patients had an overall 4.8% BMD increase, largely accounted for by a significant BMD gain in patients treated with anti-TNF α . We also observed that the baseline BMD value was independently associated with the BMD loss at the 4-year follow-up. All of the patients undergoing femoral BMD loss had proximal femur BMD > 0.8465 g/cm² at the beginning of the study. However, 4 years later, the average proximal femur BMD was similar between the two patient groups. Several explanations are possible for this observation: either the study participants plateaued at stable BMD values, having undergone BMD loss earlier in the disease course, or SpA patients with higher baseline BMD were more prone to BMD loss. Unfortunately, the absence of patient BMD values at the time of diagnosis does not allow us to refine either of these hypotheses.

Several clinical trials have previously demonstrated that anti-TNF α therapy not only prevents the BMD loss, but may

Table 4 – Follow-up BASDAI score and inflammatory factors as surrogate markers of BMD loss (N = 41).

	Sens. [%, 95% CI]	Spec. [%, 95% CI]	PPV [%, 95% CI]	NPV [%, 95% CI]	AUC, mean $\pm$ SEM [95% CI]
BASDAI ≥ 4.75	90.9 [58.7–99.8]	63.3 [43.9–80.1]	47.6 [25.7–70.2]	95.0 [75.1–99.9]	0.745 $\pm$ 0.080 [0.589; 0.901]
ESR ≥ 29 mm/h	81.8 [48.2–97.7]	73.3 [54.1–87.7]	52.9 [27.8–77.0]	91.7 [73.0–99.0]	0.759 $\pm$ 0.089 [0.586; 0.933]
CRP ≥ 15.6 mg/L	90.9 [58.7–99.8]	70.0 [50.6–85.3]	52.6 [28.9–75.6]	95.5 [77.2–99.9]	0.830 $\pm$ 0.085 [0.664; 0.997]

AUC, area under curve; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C, reactive protein; ESR, erythrocyte sedimentation rate; NPV, negative predictive value; PPV, positive predictive value; SEM, standard error of the mean; Sens., sensitivity; Spec., specificity.

also stimulate the BMD increase in SpA patients [12,31,32]. Similarly, in our study anti-TNF α therapy was associated with increased BMD (overall 5.6% gain). The majority (95%) of the patients, treated with anti-TNF α , had either stable or increased BMD. Meanwhile, the absence of anti-TNF α therapy was associated with significantly higher BMD loss. The one patient treated with anti-TNF α , who had BMD loss, began biological therapy only two months before the follow-up and, perhaps did not have enough time for the biological therapy to have a positive effect on BMD. Furthermore, our findings suggest that the evidence of previous or on-going anti-TNF α therapy could be used to exclude the need for DXA scan (NPV = 95%). Interestingly, our study did not demonstrate any relationship between BMD loss and the use of glucocorticoids, which are commonly used for treating rheumatologic diseases and are well-established contributors to osteoporosis [2,33,34].

Similarly to anti-TNF α therapy, several other follow-up factors showed promise to act as reasonable surrogate markers for BMD changes [8,10–14]. It is generally accepted that inflammation is responsible for the BMD loss in SpA patients. However, the predictive value of inflammatory factors in diagnosing the BMD loss in SpA patients remains elusive [8,31]. In our study, elevated ESR and CRP levels were among the most reliable indicators of BMD loss. Indeed, wide accessibility and high sensitivity of ESR and CRP tests makes them promising screening tools, facilitating patient selection for the DXA scan. However, the accuracy of CRP/ESR tests for BMD loss decreases in the background of other pro-inflammatory conditions, thus limiting the use of these tests in the setting of underlying infection. Bone turnover proteins, such as carboxy terminal cross-linked telopeptides of type I/II collagen, osteocalcin and bone-specific alkaline phosphatase, circumvent the challenges posed by non-specific inflammation and have recently received substantial interest as potential markers of BMD loss. However, at present the exact relationship between the BMD loss and bone turnover proteins remains elusive, preventing their wider utilization in clinical practice [12,35–37].

We believed that non-interventional tests can be used to increase the pre-test probability for BMD loss before performing a DXA scan. In agreement with previous cross-sectional studies, we found that high disease activity, as reflected by higher BASDAI and PAGDA scores and higher serum levels of inflammatory markers, are associated with BMD loss [11–13]. Although, at the beginning of the study, the differences in BASDAI score did not correlate with BMD, at 4-year follow-up BASDAI > 4.75 indicated BMD loss (Sens. 91%, Spec. 62%). In addition, raised follow-up PAGDA score was found to be a specific marker of BMD loss (sens. 45%, spec. 97%). In our study, baseline BMD and follow-up CRP values allowed us to correctly identify BMD status in 85% of cases and deserves further investigation as a follow-up strategy.

The spine mobility tests are a simple mode of measuring the patient's functional status in SpA. Some studies reported that spine mobility tests can be associated with both radiological lumbar spine damage and vertebral fractures [8,38]. Our earlier study showed that BMD reduction at both, lumbar spine and proximal femurs, is associated with decreased SpA patient mobility. Intermalleolar distance was found to have the greatest correlation with BMD changes in both spine and proximal femurs [39].

In our current longitudinal study, we found that deterioration in intermalleolar distance and lateral flexion from baseline values was associated with the BMD loss. At follow-up stable or improved lateral flexion and intermalleolar distance are both reassuring findings and might be used to exclude both the BMD loss and the need for a DXA scan (NPV = 0.88 and NPV = 0.87, respectively). The results of other spinal mobility tests, including modified Schober's tests and tragus to wall distance, failed to demonstrate any association with BMD change.

There were some limitations in our study. The number of patients in the study was relatively low and larger populations would be desirable in other prospective studies. In addition, our findings are quite specific to the study population, which had a mean of 40.9 $\pm$ 10.5 years of age (at the start of the study) and was recruited on average 5 years after the SpA diagnosis. Also, during the 4-year period the BMD changes did not correlate with fractures as no osteoporotic fractures were observed in the study population. Finally, the proposed markers are only applicable for the management of bone mineral density and not for other manifestations of spondyloarthropathies, for which regular clinical surveillance may be required.

4. Conclusions

While a DXA scan is a gold standard for BMD estimation and might be easily accessible in wealthier countries, less-resource intensive ways to assess the BMD loss and risk of pathological fractures are also needed. Baseline BMD, anti-TNF α treatment history, PAGDA score, spinal mobility tests and disease activity indices are cheap and useful markers in predicting the BMD loss in SpA patients. Clinicians may consider these factors when assessing the fracture risk in any SpA patient.

Conflicts of interest

None of the authors has any conflict of interest.

Acknowledgements

We would like to thank Centre for Evidence-Based Medicine at Vilnius University for reviewing and editing this article. Also we thank Irena Žukauskaitė, PhD, for her statistical editorial assistance.

REFERENCES

- [1] Fujita T, Matsui T, Nakao Y, Shiozawa S, Imai Y. Cytokines and osteoporosis. *Ann NY Acad Sci* 1990;587:371–5.
- [2] Gratacos J, Collado A, Pons F, Osaba M, Sanmarti R, Roque M, et al. Significant loss of bone mass in patients with early, active ankylosing spondylitis: a followup study. *Arthritis Rheum* 1999;42(11):2319–24.
- [3] Bessant R, Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? *J Rheumatol* 2002;29(7):1511–9.

- [4] van der Weijden MA, Claushuis TA, Nazari T, Lems WF, Dijkmans BA, 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(11):1529–35.
- [5] Venceviciene L, Vencevicius R, Butrimiene I. Bone mineral density changes in patients with spondyloarthropathies. In: Bruges-Armas J, editor. *Clinical and molecular advances in ankylosing spondylitis*. 1st ed. Rijeka: InTech; 2012. <http://dx.doi.org/10.5772/31335> [chapter 3]
- [6] Ulu MA, Cevik R, Dilek B. Comparison of PA spine, lateral spine, and femoral BMD measurements to determine bone loss in ankylosing spondylitis. *Rheumatol Int* 2013;33(7):1705–11.
- [7] Ralston SH, Urquhart GD, Brzeski M, Sturrock RD. Prevalence of vertebral compression fractures due to osteoporosis in ankylosing spondylitis. *BMJ* 1990;300(6724):563–5.
- [8] Klingberg E, Geijer M, Gothlin J, Mellstrom D, Lorentzon M, Hilme E, et al. Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. *J Rheumatol* 2012;39(10):1987–95.
- [9] El Maghraoui A, Do Santos Zounon AA, Jroundi I, Nouijai A, Ghazi M, Achemlal L, et al. Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice. *Osteoporosis Int* 2005;16(12):1742–8.
- [10] van der Weijden MA, van Denderen JC, Lems WF, Heymans MW, Dijkmans BA, van der Horst-Bruinsma IE. Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. *Clin Rheumatol* 2011;30(4):497–503.
- [11] Mermerci Baskan B, Pekin Dogan Y, Sivas F, Bodur H, Ozoran K. The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis. *Rheumatol Int* 2010;30(3):375–81.
- [12] Arends S, Spoorenberg A, Bruyn GA, Houtman PM, Leijnsma MK, Kallenberg CG, et al. The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. *Osteoporosis Int* 2011;22(5):1431–9.
- [13] Ghazlani 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(5):772–6.
- [14] Grazio S, Kusic Z, Cvijetic S, Grubisic F, Balenovic A, Nemcic T, et al. Relationship of bone mineral density with disease activity and functional ability in patients with ankylosing spondylitis: a cross-sectional study. *Rheumatol Int* 2012;32(9):2801–8.
- [15] Vosse D, Landewe R, Garnero P, van der Heijde D, van der Linden S, Geusens P. Association of markers of bone- and cartilage-degradation with radiological changes at baseline and after 2 years follow-up in patients with ankylosing spondylitis. *Rheumatology* 2008;47(8):1219–22.
- [16] Visvanathan S, van der Heijde D, Deodhar A, Wagner C, Baker DG, Han J, 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(2):175–82.
- [17] Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34(10):1218–27.
- [18] Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis Int* 2013;24(1):23–57.
- [19] Pile KD, Laurent MR, Salmond CE, Best MJ, Pyle EA, Moloney RO. Clinical assessment of ankylosing spondylitis: a study of observer variation in spinal measurements. *Br J Rheumatol* 1991;30(1):29–34.
- [20] Spoorenberg A, van der Heijde D, Dougados M, de Vlam K, Mielants H, van de Tempel H, et al. Reliability of self assessed joint counts in ankylosing spondylitis. *Ann Rheum Dis* 2002;61(9):799–803.
- [21] van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, Braun J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum* 2005;52(2):386–94.
- [22] van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. *Assessments in Ankylosing Spondylitis*. *J Rheumatol* 1999;26(4):951–4.
- [23] López-Larrea C, Díaz-Peña R. *Molecular Mechanisms of Spondyloarthropathies*. Landes Bioscience; 2009.
- [24] 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(12):2286–91.
- [25] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21(12):2281–5.
- [26] Daltroy LH, Larson MG, Roberts NW, Liang MH. A modification of the Health Assessment Questionnaire for the spondyloarthropathies. *J Rheumatol* 1990;17(7):946–50.
- [27] 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(6):470–6.
- [28] Jun JB, Joo KB, Her MY, Kim TH, Bae SC, Yoo DH, et al. Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. *J Rheumatol* 2006;33(8):1637–41.
- [29] Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs Jr RW, Lentle BC. Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. *J Clin Densitom* 2005;8(4):371–8.
- [30] 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(10):2205–9.
- [31] Kang KY, Ju JH, Park SH, Kim HY. The paradoxical effects of TNF inhibitors on bone mineral density and radiographic progression in patients with ankylosing spondylitis. *Rheumatology* 2013;52(4):718–26.
- [32] Kang KY, Lee KY, Kwok SK, Ju JH, Park KS, Hong YS, et al. The change of bone mineral density according to treatment agents in patients with ankylosing spondylitis. *Joint Bone Spine* 2011;78(2):188–93.
- [33] Seibel MJ, Cooper MS, Zhou H. Glucocorticoid-induced osteoporosis: mechanisms, management, and future perspectives. *Lancet Diabetes Endocrinol* 2013;1(1):59–70.
- [34] Baek HJ, Kang SW, Lee YJ, Shin KC, Lee EB, Yoo CD, et al. Osteopenia in men with mild and severe ankylosing spondylitis. *Rheumatol Int* 2005;26(1):30–4.
- [35] Muntean L, Rojas-Vargas M, Font P, Simon SP, Rednic S, Schiotis R, et al. Relative value of the lumbar spine and hip bone mineral density and bone turnover markers in men

- with ankylosing spondylitis. *Clin Rheumatol* 2011;30(5): 691–5.
- [36] Park MC, Chung SJ, Park YB, Lee SK. Bone and cartilage turnover markers, bone mineral density, and radiographic damage in men with ankylosing spondylitis. *Yonsei Med J* 2008;49(2):288–94.
- [37] Borman P, Babaoglu S, Gur G, Bingol S, Bodur H. Bone mineral density and bone turnover in patients with psoriatic arthritis. *Clin Rheumatol* 2008;27(4): 443–7.
- [38] Wanders A, Landewe R, Dougados M, Mielants H, van der Linden S, van der Heijde D. Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: can assessment of spinal mobility be a proxy for radiographic evaluation? *Ann Rheum Dis* 2005;64(7):988–94.
- [39] Vencevičienė L, Butrimienė I, Venalis A. Relationship between functional disability and bone loss in spondyloarthropathy patients. *Duzce Univ Med Fac J* 2009;11(2):1–8.