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RELATIONSHIP OF BONE MINERAL DENSITY WITH DISEASE ACTIVITY AND FUNCTIONAL ABILITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS: A CROSS SECTIONAL STUDY

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Summary

Aim. In ankylosing spondylitis (AS) inflammatory activity probably plays a key role in the pathophysiology of bone loss. The aim of the study was to investigate the relationship of bone mineral density (BMD) at the lumbar spine and hip region with some measures of disease activity and functional ability in patients with ankylosing spondylitis.

Methods: In 80 patients with established ankylosing spondylitis disease activity and functional ability were determined by C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). Spinal pain and patient global health were assessed using horizontal visual analogue scale (VAS). BMD was measured by dual-energy x-ray absorptiometry (DXA).

Results. There was a significant negative correlation of bone density T scores with acute phase reactants (i.e. patients with lower T scores had higher level of CRP and ESR). That relationship was reflected more reliably at proximal femur sites than at the lumbar spine. There were also significant differences in ESR, BASDAI, BASFI, spinal pain and global health between three groups of patients according to WHO classification of osteoporosis

(normal, osteopenic and osteoporotic). Significantly more patients with osteopenia at the lumbar spine had lower BASDAI index than those with normal BMD (p=0.030).
Conclusion: Our results indicate an association of low BMD with high disease activity in patients with AS. Femoral BMD seems to be more associated with disease activity and functional ability than lumbar spine BMD.

Key words: ankylosing spondylitis, bone mineral density, disease activity, functional ability

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease which predominantly affects the spine, sacroiliac joints and entheses. The etiology is not fully understood, but there is a strong genetic predisposition associated with human leukocyte antigen (HLA)-B27 [1]. The primary disease localization is considered to be the enthesitis, but the hallmark of advanced AS is spine ankylosis (syndesmophytes) related to new bone formation. Although seemingly contrasted to bone formation osteoporosis (OP) is a well known feature of AS, with some differences in severity, probably depending on the AS stage. Accordingly, osteoporotic fractures are more prevalent in patients with AS than in the general population [2-4]. Due to the formation of paravertebral calcification false interpretation of spine bone density measured by dual-energy x-ray absorptiometry (DXA) can occur.

In AS the relative contribution of different factors commonly implicated in bone mineral disorders and also observed in other inflammatory arthritides, such as inflammatory process, decreased mobility and/or changed hormone status is still controversial. Osteopenia was observed in patients with clinically severe AS, but also in those with mild AS with little mobility limitation [5].

As the question still remains whether the bone loss in AS is primarily the result of inflammatory activity or even limited mobility, the aim of the study was to examine relationship of bone mineral density with disease activity and functional ability in patients with AS. We also investigated the difference in that relationship between different skeletal sites.

Patients and methods

Patients

Eighty ambulatory, community-dwelling patients fulfilling the modified New York criteria were randomly assigned from database of 217 patients from the Rheumatology Clinic. The letter of invitation to participate in the study was sent to one hundred patients. The selection included those who have not received systemic glucocorticoids or any other drug that might influence bone mass or, according to medical record, had no disease or condition that affect bone metabolism (i.e. hyperparathyreoidism, hyperthyreosis, hepatic or renal failure, alcoholism, malnutrition). Also, none of the subjects had a hip replacement. Eighty patients responded to the invitation (response rate of 80%). Sixty-seven patients (86%) were HLA B 27 antigen positive.

Prior to inclusion to the study, an informed consent was obtained from all participants.

The study was approved by the Ethics Committee of the Clinical Hospital "Sisters of Mercy" in Zagreb and was performed in accordance with ethics standards of the 1964 Declaration of Helsinki [6].

Data collection/Measurement

Age and the duration of disease were retrospectively collected from the patients' medical record. All subjects underwent thorough physical examination. Subjects were interviewed by investigators experienced in epidemiological research (SG, FG). Functional status and measures of disease activity and severity were obtained using established methods. Functional ability was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI) [7]. BASFI is a set of 10 questions designed to determine the degree of functional limitation in AS. It is a self-assessment tool where a 100 mm horizontal visual analogue scale (VAS) is used to answer the questions that reflect the ability to perform specific tasks. The mean of the ten scales gives the BASFI score, value between 0 and 100. Disease activity was measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [8]. The BASDAI is also a self-assessment tool that evaluates a range of symptoms. Like the BASFI , the BASDAI consists of 100 mm horizontal VAS used to answer 6 questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, pain and swelling in other joints, discomfort with peripheral entheses and severity and duration of morning stiffness. To give each symptom equal weighting, the mean of two scores relating to morning stiffness is taken. The resulting score is then divided by 5 to give the final BASDAI score (0-100). Croatian versions of BASDAI and BASFI scores proved to be reliable and valid [9].

Inflammatory activity was also measured by erythrocyte sedimentation rate (ESR, Westergren's method, normal values in men <15mm/h and in women <20mm/h) and C-reactive protein (CRP, ELISA, normal values <5 mg/L).

Spinal pain and patient global assessment of the global health were estimated using a 100 mm horizontal VAS.

Bone mineral density (g/cm^2) at the lumbar spine (L2-L4) and at the left hip (total hip and femoral neck) was measured by dual-energy x-ray absorptiometry (DXA, Hologic, QDR 4500, USA). Calibration with a lumbar spine phantom is performed weekly. Bone mineral density of the femoral neck is included in the DXA measurement because it is recognized as very important in predicting risk for osteoporotic fractures (including the newest FRAX - fracture-risk calculator) and the results are rarely influenced by osteophytes and other degenerative changes [10,11].

Patients were classified as having osteoporosis according to the WHO criteria: osteoporosis if T score was less than -2.5 SD, osteopenia if T score was between -1.0 to -2.5 SD and normal T score if values were better than -1.0 SD [12]. As many people experience osteoporotic fracture without the BMD being below a threshold for osteoporosis i.e. in osteopenic range [13], patients were also classified in two categories according to their bone density status: those with normal T score (> -1) or pathological T-score ($\leq$ -1; osteopenia and osteoporosis).

Statistics

Apart from descriptive statistics data were analyzed by Student t-test, Pearson correlation, one way-ANOVA and non-parametric Kruskal-Wallis test. Bivariate correlations were calculated using Pearson correlation (T scores in each of 3 regions were correlated with age, duration of the disease, BASFI, BASDAI, pain, global health, ESR or CRP). The comparisons were performed using Student t-test (two categories of bone density status with BASFI, BASDAI, pain, global health, ESR or CRP) and one way-ANOVA (including post-hoc analysis) for WHO classification of osteoporosis with formerly mentioned continuous variables. ANOVA was used to test the differences in bone mineral density between three groups of patients. F value represents the ratio of the between-group variation divided by the within-group variation. A large F evidences that there are more differences between groups than within groups. As F goes up, p value goes down.

According to the result of the homogeneity of variances, in some cases the Kruskal-Wallis test was performed in association with the following variables: two categories of bone density status or WHO classification of osteoporosis status for lumbar spine with BASFI and CRP; for total hip with ESR and CRP; and for femoral neck with CRP. Informatively, eta-coefficients were calculated to correlate categorical variables (T score according WHO classification of osteoporosis and two categories of bone density status in each of 3 regions) with the most important continuous variables (BASFI and BASDAI), too. All the statistics was made using SPSS/PC ver.13.0 software. The level of significance was set at $p<0.05$.

Results

There were 46 men and 34 women who participated in the study. The mean age of subjects was 52.3±10.3 years and the mean duration of the disease was 21.8±10.3 years. Other clinical characteristics are presented in Table 1. Fifty five subjects (69%) had clinical signs of enthesitis.

There were significantly more patients classified as osteoporotic at the lumbar spine than at the total hip (p=0.016) (Table 2). However, there were significantly more patients with osteopenia at the femoral neck than at the spine (p=0.001).

Correlation analyses (Table 3) showed that lower lumbar spine and femoral neck T scores were associated with higher spinal pain (p=0.027 for lumbar spine; p=0.030 for femoral neck), and the same negative correlation was found for lumbar spine T score and global health (p=0.004). T scores were also significantly negatively correlated with CRP (p=0.006 lumbar spine; p=0.042 total hip; p=0.000 femoral neck) and ESR (p=0.010 lumbar spine; p=0.006 femoral neck).

Analysis of differences in clinical and laboratory parameters of interest between three groups of patients according to WHO classification of osteoporosis revealed a significant difference in BASDAI (p=0.011), ESR (p=0.032), spinal pain (p=0.002) and global health perception (p=0.017) between them regarding their osteoporosis status in lumbar spine. There was a significant differences in BASFI (p=0.004), spinal pain (p=0.000) and global health perception (p=0.006) between the groups of patients according to the osteoporosis status in total hip, too. Spinal pain was the only item significantly different between patients who had osteopenia, osteoporosis or normal BMD in femoral neck (p=0.019). In one way ANOVA analysis BASFI did not show a difference between 3 WHO categories at the lumbar spine (p=0.181), as BASDAI at the hip region. Post hoc analysis showed that significantly more patients with osteopenia at lumbar spine had lower BASDAI than those with normal BMD (p=0.030), while there was a borderline difference between patients with osteoporosis and osteopenia (p=0.055). Using more strict Scheffe's test the difference in BASDAI between normal and osteopenic patients was even more significant (p=0.012). BASDAI was not influenced by age (p=0.601) or by duration of the disease (p=0.330).

Non-parametric test analysis also showed a significant difference in CRP and ESR between groups of patients according to the WHO classification of osteoporosis status, with higher levels of acute phase parameters in subjects with lower T score (CRP: p=0.046 lumbar spine, p=0.020 total hip and p=0.07 femoral neck; ESR: p=0.004 total hip).

When grouping subjects into two BMD categories (normal or pathological), subjects with pathological T score at the lumbar spine had higher BASDAI (p=0.021), level of spinal pain (p=0.012), global health (p=0.006), as well as higher ESR (p=0.007). The difference between

groups with normal and pathological femoral T scores was found in BASFI (p=0.036), spinal pain (p=0.001) and global health (p=0.004). Non-parametric test for omitted variables showed the differences in two categories of osteoporosis status in lumbar spine with CRP (p=0.044), of total hip with ESR (p=0.017) or CRP (p=0.001) and in femoral neck with CRP (p=0.020).

Discussion

The aim of our study was to investigate whether osteopenia and osteoporosis are a consequence of inflammation or a consequence of limited mobility, measured through functional inability and thus an indirect consequence of inflammation. The results of our study showed a correlation of bone mineral density with disease activity and functional ability in patients with AS. Also, in our study the relationship between disease activity indices and bone density status was more significant at the femoral neck than at the lumbar spine.

Although epidemiologic studies showed that proinflammatory cytokines were associated with decreased bone mass the overall evidence is still limited. Inflammation may influence bone metabolism due to the effect of pro-inflammatory mediators such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha, which play an important role in bone loss through their effect on osteoclast activity [14]. The most suggestive findings that inflammation contributes to bone loss in the spine come indirectly from studies confirming that in patients receiving anti TNF therapy there is not only a significant improvement of symptoms and a decrease of inflammation, but also an increase in BMD [15-18].

There is evidence that pro-inflammatory cytokines have been associated with bone resorption in other inflammatory rheumatic diseases. In patients with rheumatoid arthritis, elevated acute-phase reactants have been correlated with lower BMD and higher bone turnover [19]. A statistically significant difference in ESR and CRP between patients with familial Mediterranean fever and controls has also been observed [20]. Osteoclastic bone resorption in those diseases was associated with increased production of pro-inflammatory cytokines. Moreover, estrogen withdrawal is associated with increased production of pro-inflammatory cytokines. However, in AS few erosions are observed, with exception of the anterior corners of the vertebral bodies and the sacroiliitis, suggesting that different mechanisms underline the bone loss in AS. There is still a question regarding temporal sequences of systemic inflammation, bone resorption and bone formation in AS and the underlying pathway include bone morphogenic proteins (BMPs), sclerostin and molecules of wingless-type (Wnt) pathway such as /β-catenin [21]. Understanding of these mechanisms would elucidate the uncoupling of osteoporosis and structural changes (i.e. bone formation) in AS. Nevertheless, our results are in favour of the existence of a relationship between inflammation activity and osteoporosis in patients with AS.

Additionally for the assessment of clinical disease activity and functional limitation we used two generally accepted questionnaires specifically designed for patients with AS, (BASFI, BASDAI). The Bath AS Indices are widely used to evaluate function, spinal mobility, and disease activity. These questionnaires reflect the entire spectrum of the disease and are sensitive to clinical changes [7,8]. In our study they were also significantly correlated with

bone density status. The patient's assessment of global health and spinal pain were also used and comparing to BASFI and BASDAI they were even more strongly related to the bone density status.

Although we found a negative correlation between bone density and disease activity (CRP, ESR) i.e. lower bone density correlated with higher disease activity, post hoc analysis showed a lower BASDAI in the group with osteopenia compared to the group with normal BMD at lumbar spine. This might be due to the statistical analysis on relatively small number of patients with osteopenia (n=16), especially comparing to normal BMD (n=44). Nevertheless, when splitting subjects into two BMD categories, normal and pathological (osteopenia and osteoporosis), those with pathological T score had a higher BASDAI, indicating an expected direction of overall correlation between these two variables.

There are other studies which also showed the same relationship between disease activity parameters (ESR, CRP levels and BASDAI) and bone density indicating that bone loss in AS is predominantly the consequence of inflammatory mediators' action [22-26].

In a recent paper Ghozlani et al found that BASDAI, together with the disease duration and body mass index, was associated with osteoporosis in patients with AS [23]. But there are some studies in which a correlation between disease activity parameters and BMD could not been established [27]. The negative results may be explained by the fact that inflammation parameters were determined at the one point of time. Moreover, BASDAI does not reflect only inflammation as pain and other symptoms can arise from other causes, too. However, only a limited number of studies analyzed both BASDAI and BASFI with bone density in patients with AS and like in our study, they confirmed their significant correlation with bone density [22].

Consistently with that, laboratory disease activity indicators, ESR and CRP were significantly correlated with bone density status in our patients, which support the notion that higher disease activity facilitates the developing of osteoporosis in AS. Those results were confirmed with the tests of difference, which showed significant difference in ESR and CRP between patients with normal or pathological bone density. It should be kept in mind that the evaluation of disease activity in AS using ESR and CRP is somewhat difficult. That is, regardless of the elevated ESR or CRP in majority of patients with active AS, there is a lack of their clear correlation with clinical disease activity [28]. Even though the ESR and CRP levels does not always coincide with activity of AS, their association with osteoporosis has been observed in other similar studies. Baskan et al with an even wider programme found a significant negative correlation of the bone density with ESR and CRP levels, as well as with BASMI and non-significant correlation between CRP and BASDAI [22]. Generally, our results are in the accordance with these results.

Moreover, as for fractures Przepiera-Bedzak et al observed an increased relative risk of fractures in patients with increased level of CRP [29].

In our study group, the osteoporosis was slightly more prevalent at the lumbar spine than at the hip region. Nearly 25% of patients had spinal osteoporosis despite the presence of syndesmphytes as the consequence of the advanced disease. Apart from inflammation possible explanation of the latter might be that trabecular bone of vertebral bodies is metabolically more active and thus more susceptible to cytokine and hormone influences than cortical bone which is predominant in the proximal femur. Considering the prevalence of osteoporosis in AS, the results from other studies showed its existence in 14% to 34.3% of patients at the lumbar spine and between 11% to 29% at the hip [23,30-33]. So, consistently with our study other investigators also found higher prevalence of osteoporosis of the spine compared to the hip region. Capaci et al. found that even 61.6% of patients with mild AS had spinal osteoporosis and osteopenia, while 46.6% had osteoporosis and osteopenia at the total hip [34].

We did not exclude the subjects whose thoraco-lumbar spine radiographs showed syndesmophytes or ankylosis of the posterior interapophyseal joints. It is presumed that in longstanding AS, the level of osteopenia at the lumbar spine could be masked due to the structural alteration of the vertebral bodies and to new bone formation, so the bone loss may not always be apparent [35]. In other words the correlation between disease duration and increased spine bone density might result from syndesmophytes [22]. Therefore, it is proposed that the proximal femur, and particularly the femoral neck should be used to evaluate bone mass in patients with AS, because the result of DXA measurement is not disturbed by osteophytes and of interest is also that this is the region where the hip fracture often occurs [24].

Osteoporosis can be, at least partly, a consequence of reduced physical activity, while specifically decreased spinal mobility and reduced chest expansion might be responsible for the difference between spine and hip BMD. In accordance with that we previously reported on the relationship between a decreased mobility of thoracic and lumbar spine and the chest expansion index in patients with a lower T score in lumbar and hip region [36].

Apart from a cross-sectional design the limitation of this study is the lack of data for bone turnover markers, parathyroide hormone or vitamin D3, which could have revealed a better insight of association between activity parameters of both osteoporosis and AS [37,38]. Although we found the correlation between bone density with disease activity and BASFI, the additional limitation of our study is that we did not formally analyse radiological changes of the spine or sacroiliac joints using any scoring method (for instance SASSS), nor investigated mobility using validated metrological index (for instance BASMI). We could not adequately

address possible association of parameters of interest in the early (preradiological) stage of the disease as our group of patients had a long lasting disease (median around 10 years).

However, in our study we had data comprised on of relevant parameters of disease activity (ESR, CRP, BASDAI) and functional ability (BASFI), so the association between bone density status with disease activity and functional ability in AS was analyzed with objective and standardized parameters. Moreover, the group of subjects we investigated was homogenous regarding the inclusion criteria, where only the patients with confirmed diagnosis of AS who met the modified New York criteria were eligible for the study.

Conclusions

In our sample of subjects with established and long-lasting AS we found a significant negative correlation of the bone density with CRP and ESR and a non-significant correlation of the bone density with BASDAI and BASFI. As there is an association between high disease activity with osteoporosis in, we can assume that osteoporosis in AS is primarily consequence of inflammation. Osteoporosis status at hip seems to be more associated with functional ability and also with inflammatory activity of the disease than at the lumbar spine. Despite of that, osteoporosis was more prevalent in spine than in hip, regardless the ossification of the spine in AS. Therefore, apart from femoral neck BMD it would be important to perform regular BMD measurement of axial skeleton (lumbar spine) in patients with AS, too.

Conflict of interest

The authors declare that they have no conflict of interest.

Literature

1. Thomas GP, Brown MA (2010) Genetics and genomics of ankylosing spondylitis. Immunolog Rev 233:162-80
2. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Falon WM, Melton J (1994) Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 21:1877-82
3. Hunter T, Dubo HIC (1983) Spinal fractures complicating ankylosing spondylitis: a long-term follow-up study. Arthritis Rheum 26:751-9
4. Ralston SH, Urquhart GDK, Brzeski M, Sturrock RD (1990) Prevalence of vertebral compression fractures due to osteoporosis in ankylosing spondylitis. BMJ 300:563-5
5. Baek HJ, Kang SW, Lee YJ et al (2005) Osteopenia in men with mild and severe ankylosing spondylitis. Rheumatol Int 26:30-4
6. World Medical Organization. Declaration of Helsinki (1996) British Medical Journal (7 December) 313(7070):1448-9
7. Calin A, Garrett S, Whitelock H et al (1994) A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 21:2281-5
8. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A (1994) A new approach to defining disease status in ankylosing spondylitis: the Bath Anyklosing Spondylitis Disease activity Index. J Rheumatol 21:2286-91
9. Grazio S, Grubišić F, Nemčić T, Matijević V, Skala H (2009) The reliability and validity of a Croatian version of the Bath Ankylosing Spondylitis Functional Index and Bath Ankylosing Spondylitis Disease Activity Index in patients with ankylosing spondylitis. Reumatizam 56:63-76 (article in Croatian)
10. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A (2000) Risk of hip fracture according to World Health Organization criteria for osteoporosis and osteopenia. Bone 27:585-90
11. FRAX ^{TM} and the assessment of fracture probability in men and women from the UK (2008) Osteoporosis Int 19:385-97
12. WHO. Report of a WHO Study Group, World Health Organ Tech Rep (1994) Ser, 843
13. Siris ES, Chen YT, Abbott TA et al (2004) Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med. 164:1108-12
14. McDonald BR, Gowen M (1992) Cytokines and bone. Br J Rheumatol 31:149-55.
15. Briot K, Gossec L, Kolta S, Dougados M, Roux C (2008) Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-alpha treatment. J Rheumatol 35:855-61
16. Barnabe C, Hanley DA (2009) Effect of tumor necrosis factor alpha inhibition on bone density and turnover markers in patients with rheumatoid arthritis and spondyloarthropathy. Semin Arthritis Rheum 39:116-22
17. Visvanathan S, van der Heijde D, Deodhar A et al (2009) Effects of infliximab on markers of inflammation and bone turnover and associations with bone mineral density in patients with ankylosing spondylitis. Ann Rheum Dis 68:175–82
18. Allali F, Breban M, Porcher R, Maillefert JF, Dougados M, Roux C (2003) Increase in bone mineral density of patients with spondyloarthropathy treated with anti-tumour necrosis factor alpha. Ann Rheum Dis 62:347–9

19. Laan R, Buijs W, Draad M et al (1991) Bone mineral density in rheumatoid arthritis: influence of disease activity and functional capacity. Arthritis Rheum 34:S180
20. Yildirim K, Karatay S, Cetinkaya R et al (2009) Bone mineral density in patients with familial Mediterranean fever. Rheumatol Int 30:305-8
21. Sieper J (2009) Can structural damage be prevented in ankylosing spondylitis? Curr Opin Rheumatol 21:335-9
22. Başkan BM, Doğan YP, Sivas F, Bodur H, Özoran K (2010) The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis. Rheumatol Int 30:375-81
23. Ghozlani I, Ghazi M, Nouijai A et al (2009) Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. Bone 44:772-6
24. Gratacos J, Collado A, Pons F et al (1999) Significant loss of bone mass in patients with early, active ankylosing spondylitis: a follow-up study. Arthritis Rheum 42:2319-24.
25. Incel NA, Gokoglu F, Nacir B, Incel N (2006) Bone and stone in ankylosing spondylitis: osteoporosis and urolithiasis. Clin Rheumatol 25:667-70.
26. Lange U, Teichmann J, Strunk J, Müller-Ladner U, Schmidt KL (2005) Association of 1.25 vitamin D3 deficiency, disease activity and low bone mass in ankylosing spondylitis. Osteoporos Int 16:1999-2004
27. Toussirot E, Michel F, Wendling D (2001) Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology 40:882-8
28. Ozgocmen S, Godekmerdan A, Ozkurt-Zengin F (2007) Acute-phase response, clinical measures and disease activity in ankylosing spondylitis. Joint Bone Spine 74:249-53
29. Przepiera-Bedzak H (2007) The value of researches, which assess bone mineral density and bone metabolism in patients with ankylosing spondylitis, in detecting osteoporosis. Ann Academ Med Stetinen 53:39-47 (article in Polish)
30. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J (2005) Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. J Rheumatol 32:1290-8
31. Toussirot E, Wendling D (2000) Bone mass in ankylosing sponylitis. Clin Exp Rheumatol 18(suppl 21):S16-S20
32. Borman P (2004) Functional disability and quality of life in patients with ankylosing spondylitis. Rheumatol Int24:59-60
33. El Maghraoui A (2004) Osteoporosis and ankylosing spondylitis. Joint Bone Spine 71:291-5
34. Capaci K, Hepguler S, Argin M, Tas I (2003) Bone mineral density in mild and advanced ankylosing spondylitis. Yonsei Med J 44(3):379-84
35. Mitra D, Elvins DM, Speden DJ, Collins AJ (2000) The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. Rheumatology 39:85-9
36. Grubišić F, Grazio S, Balenović A, Nemčić T, Kusić Z (2009) Osteoporosis, spinal mobility and chest expansion index in patients with ankylosing spondylitis. Coll Antrop (accepted for publication).
37. Sarikaya S, Basaran A, Tekin Y, Ozdolap S, Ortancil O (2007) Is osteoporosis generalized or localized to central skeleton in ankylosing spondylitis? J Clin Rheumatol. 13:20-4.

38. Lange U, Jung O, Teichmann J, Neeck G (2001) Relationship between disease activity and serum levels of vitamin D metabolites and parathyroid hormone in ankylosing spondylitis. Osteoporos Int 12:1031-5

Table 1. Basic characteristics of subjects (N=80).

Variables	**Mean ± SD**
Age (years)	52.3 ± 10.3
Disease duration (years)	21.8 ± 10.3
BASFI (score 0-100)	50.3 ± 24.4
BASDAI (score 0-100)	54.4 ± 23.2
ESR (mm/h)	22.2 ± 20.8
CRP (mg/L)	12.6 ± 18.3
Spinal pain (score 0-100)	39.5 ± 22.4
Patient global assessment (PGA) (score 0-100)	43.0 ± 26.0
Chest expansion index (cm)	3.1±1.6

Table 2. Distribution of patients according to WHO classification of osteoporosis

WHO classification of osteoporosis	**Lumbar spine N (%)**	**Hip (total) N (%)**	**Hip (femoral neck) N (%)**
Normal	44 (55.0 %)[a]	53 (66.3%)	24 (30.0%)
Osteopenia	16 (20.0%)[a]	21 (26.2%)	38 (47.5%)
Osteoporosis	20 (25.0%)[b]	6 (7.5%)	18 (22.5%)

a p=0.001 lumbar spine : femoral neck (t-test)

b p=0.016 lumbar spine: total hip (t-test)

Table 3. Correlation matrix of major parameters of interest.

	Age (yrs.)	Disease duration (yrs.)	BASFI	BASDAI	Spinal pain (VAS)	Global health (VAS)	ESR (mm/h)	CRP (mg/L)	Lumbar spine T-score	Total hip T score
Disease duration (yrs.)	0.526									
	(0.000)									
BASFI	0.297	0.183								
	(0.008)	(0.106)								
BASDAI	0.137	0.227	0.677							
	(0.347)	(0.117)	*(0.000)*							
Spinal pain (VAS)	-0.025	-0.018	0.265	0.402						
	(0.827)	(0.877)	*(0.017)*	*(0.004)*						
Global health (VAS)	-0.058	-0.070	0.201	0.394	0.767					
	(0.611)	(0.541)	(0.074)	*(0.005)*	*(0.000)*					
ESR (mm/h)	0.047	-0.060	0.113	-0.132	0.633	0.602				
	(0.691)	(0.615)	(0.337)	(0.392)	*(0.000)*	*(0.000)*				
CRP (mg/L)	-0.158	-0.176	0.136	0.031	0.557	0.543	0.441			
	(0.187)	(0.143)	(0.254)	(0.842)	*(0.000)*	*(0.000)*	*(0.000)*			
Lumbar spine T-score	0.049	0.087	0.014	0.188	-0.251	-0.318	-0.303	-0.326		
	(0.672)	(0.450)	(0.903)	(0.201)	*(0.027)*	*(0.004)*	*(0.010)*	*(0.006)*		
Total hip T score	-0.063	-0.027	0.009	0.218	-0.136	-0.219	-0.219	-0.246	0.634	
	(0.588)	(0.820)	(0.941)	(0.136)	(0.237)	(0.056)	(0.067)	*(0.042)*	*(0.000)*	
Femoral neck T score	-0.361	-0.150	-0.197	0.129	-0.248	-0.201	-0.323	-0.418	0.574	0.592
	(0.001)	(0.195)	(0.086)	(0.386)	*(0.030)*	(0.080)	*(0.006)*	*(0.000)*	*(0.000)*	*(0.000)*

Results are presented as Pearson's coefficient of correlation and p value in brackets

Table 4. One way ANOVA results of association between WHO classification of osteoporosis in each skeletal region and BASFI, BASDAI, ESR, spinal pain or global health

	Lumbar spine		Total hip		Femoral neck	
	F	p	F	p	F	p
BASFI		0.182	6.100	*0.004*	2.232	0.114
BASDAI	4.974	*0.011*	0.248	0.782	0.624	0.540
ESR (mm/h)	3.099	*0.032*				
Spinal pain (VAS)	5.286	*0.002*	11.109	*0.000*	4.197	*0.019*
Global health (VAS)	3.639	*0.017*	5.437	*0.006*	1.301	0.279