Bone Mineral Density, Vertebral Fractures and Related Factors in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Kemik Mineral Yoğunluğu, Vertebral Fraktürler ve İlişkili Faktörler

Ayla ÇAĞLAYAN, Nurdan KOTEVOĞLU, Abdullah MAHMUTOĞLU*, Banu KURAN
*Şişli Etfal Eğitim ve Araştırma Hastanesi Fizik Tedavi ve Rehabilitasyon ve *Radyoloji Kliniği, İstanbul, Türkiye*

Summary

Objective: The aim of this study was to evaluate bone mineral density, osteoporosis and fractures in patients with ankylosing spondylitis (AS) along with related factors like depression, fatigue and quality of life.
Materials and Methods: In this prospective, controlled study 38 patients with ankylosing spondylitis and 30 healthy controls were evaluated densitometrically by DXA and quantitative ultrasonography (QUS) of the heel was performed. With the use of DXA, bone mineral densities (BMD) of the proximal femur, tibia and lateral lumbar vertebrae were determined. Dorsal and lumbar radiographs were obtained for morphometric measurements. Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), fatigue scale, Beck Depression Scale and SF-36 were used.
Results: In patients L3 t values were significantly lower than controls ($p<0.05$) with lower femoral neck and total BMD values (in terms of g/cm^2 and t-scores) ($p<0.01$) but similar tibial measurements ($p>0.05$). Femoral and tibial BMD were moderately correlated with calcaneal QUS ($r: 0.427$; $p<0.05$). Vertebral fractures were diagnosed in 21% of patients without any correlation with BMD. Osteoporosis was strongly associated with CRP, BASMI, duration of disease, age and sedimentation rate. Physical role difficulty subgroup of SF-36 was correlated with BMD of the femoral neck ($p<0.05$).
Conclusion: Calcaneal QUS and tibial BMD values also inform about femoral bone mass. Vertebral fractures can develop independently from BMD. CRP levels, sedimentation rate, and limitation in mobility play significant roles in development of osteoporosis in AS. *Turk J Phys Med Rehab 2007;53:25-9*
Key Words: Ankylosing spondylitis, osteoporosis, quality of life

Özet

Amaç: Ankilozan spondilit (AS) hastalarında kemik mineral yoğunluğunun, osteoporozun ve fraktürlerin yanısıra depresyon, yorgunluk, yaşam kalitesi gibi ilişkili faktörlerin değerlendirilmesi amaçlandı.
Gereç ve Yöntem: Bu prospektif kontrollü çalışmada 38 ankilozan spondilitli hastanın ve 30 sağlıklı kontrolün, proksimal femur, tibia ve lateral lomber vertebral kemik mineral yoğunluğu (KMY) ölçümleri DEXA ile ve kalkaneal kemik ölçümleri kantitatif ultrason ile değerlendirildi. Dorsal ve lomber radyografilerden morfometrik ölçümler yapıldı. Bath Ankilozan Spondilit Fonksiyonel İndeksi (BASFİ), Bath Ankilozan Spondilit Metroloji İndeksi (BASMİ), Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAİ), yorgunluk ölçeği, Beck Depresyon ölçeği ve SF-36 kullanıldı.
Bulgular: Hastaların femur boynu ve total KMY değerleri ile birlikte (g/cm^2, t değerleri) ($p<0,01$) L3 vertebra t değerleri kontrollerden anlamlı derecede daha düşüktü ($p<0,05$), fakat tibia ölçümleri benzerdi ($p>0,05$). Femoral ve tibial KMY, kalkaneal QUS ile orta derecede korele idi ($r: 0,427$; $p<0,05$). Hastaların %21'inde vertebra fraktürü tesbit edildi, ancak bu sonuç KMY ile korele değildi. Osteoporoz; CRP, BASMİ, hastalık süresi, yaş, sedimentasyon hızı ile kuvvetli ilişkili idi. SF-36'nın, fiziksel rol güçlüğü alt grubu, femur boynu KMY ile korele idi ($p<0,05$).
Sonuç: Kalkaneal QUS ve tibia KMY değerleri femoral kemik kitlesi hakkında bilgi verir. Vertebra fraktürü KMY'den bağımsız olarak gelişebilir. CRP düzeyi, sedimantasyon hızı ve hareket kısıtlılığı AS'de osteoporoz gelişiminde önemli rol oynar. *Türk Fiz Tıp Rehab Derg 2007;53:25-9*
Anahtar Kelimeler: Ankilozan spondilit, osteoporoz, yaşam kalitesi

Introduction

Ankylosing spondylitis (AS) with erosions in vertebral bones also causes new bone formation and ankylosis (1). Bone density in axial skeleton decreases in AS and is associated with increased vertebral fracture in the spine and femur even during the early periods of the disease (2,3). The etiology of osteoporosis in AS is related to both mechanical and biochemical factors (4). In the late stages of AS, due to Wolf's Law, diminished compression on the trabecular bone causes decreased trabecular density but in early disease, systemic factors are more important than bony structure (4). It has been shown that osteoclasts are activated by

Address for Correspondence: Dr. Nurdan Kotevoğlu, Şişli Etfal Eğitim ve Araştırma Hastanesi Fizik Tedavi ve Rehabilitasyon Kliniği, İstanbul, Türkiye
Tel.: +90 216 378 76 66 Faks: +90 216 414 68 65 E-mail: nkotevoglu@superonline.com **Accepted:** February 2007

TNF-α TNF-β and IL-1 cytokines. When compared to non-inflammatory back pain patients, TNF-α and IL-6 concentrations increase in AS patients and there is a positive correlation between TNF-α and IL-6 levels with activity and severity of the disease. Genetic factors and corticosteroid therapy are also effective on low bone mineral density in AS (4). Since more than 50% bone loss can be determined by plain X-ray it is not suitable for diagnosis of osteoporosis in AS. DXA is not reliable in all stages of AS as well. In the late stage, spine syndesmophytes can mask osteopenia at L1-L5 vertebrae and results can be false negative. Higher than expected bone densities in AS due to new bone formation have been shown even in early AS (4). Hip measurement is a more sensitive method to determine osteoporosis in advanced AS (5). In moderate and severe cases, L3 vertebral measurement at lateral decubitus position (LAT-L3) is found more sensitive than anteroposterior position (4).

In recent years, quantitative ultrasound (QUS) being cheap, portable and free from ionizing radiation has become an interesting method in evaluating bone density. Calcaneal ultrasound also measures trabecular bone density but may not reflect the density of the axial trabecular bone. Calcaneal ultrasound can also predict the osteoporotic hip fracture more precisely than spinal incidents (2,4).

In AS, fracture related to osteoporosis is more prevalent in the spine. Spinal fracture incidence is higher in the first 5 years after the diagnosis and decreases in the 2nd and 3rd decades. Fracture possibility increases with limitation of the spine, dense syndesmophytes, periphereal joint involvement (4).

Materials and Methods

According to the Modified New-York criteria (6), 38 men with AS (Group 1) and 30 healthy men (Group 2) were enrolled into this study. Patients with inflammatory bowel disease, psoriasis, neoplasms, malnutrition, parathyroid and thyroid disease and those using anticonvulsants, anticoagulants, long-term steroids (>1 month) and excessive alcohol were excluded. Demographic data (age, height, weight, body mass index) and duration of disease (period after diagnosis) were recorded.

Functional conditions of the patients were evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI). This scale evaluates 10 daily activities separately. Each question has 10 points and the score is calculated with the average of total scores (7). As score decreases, functional capacity increases. For disease activity, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used (8). In this scale fatigue, pain due to spinal and peripheral joint involvement, localized sensitivity and morning stiffness were evaluated. Both the severity and duration of morning stiffness were asked in 6 questions. Average of two question scores about morning stiffness was summed with other four scores and the total sum was divided to 5 for final result. As score decreases, activity of the disease decreases. Spine movements were evaluated with Bath Ankylosing Spondylitis Metrology Index (BASMI). Tragus-wall distance, lumbar flexion, cervical rotation, lumbar lateral flexion and intermalleolar distance were measured and scored. Total score is between 0 to 10 points (9). As mobility increases, the score decreases. For depression recently modified version of Beck Depression Scale, comprising of 13 questions was used. It is designed as a questionnaire and asks the patients to choose the most appropriate statements (10).

Fatigue was evaluated with the Multidimensional Assessment of Fatigue Scale (MAF) which was developed by Belza et al. (11) Severity and frequency of the fatigue can be evaluated in 5 dimensions considering daily functions and psychological condition. Patients were asked to evaluate the 5 questions on a 10 mm VAS. Total score is 50 and fatigue increases as score increases.

Quality of life was evaluated using the Short-Form 36 (SF-36). SF-36 is a frequently used reliable and valid health scale. It has 8 items such as physical function, social function, physical role limitation, emotional role limitation, mental health, energy, pain and general health. It is evaluated between 0 to 100 points and low score corresponds to poor condition (12) .

Serum calcium (Ca), phosphorous (P), alkaline phosphatase (ALP), parathyroid hormone and vitamin D levels and 24 hours urine levels of Ca and P were detected in order to exclude secondary causes of osteoporosis.

Bone mineral density was evaluated with Lunar-DXA. Lateral decubitus position measurements were assessed in accordance with Lunar manual analysis technique. Since Lunar was not standardized for this position, results were compared with healthy controls of the same age and gender. Due to the superpositioning of the iliac bone and ribs, lateral L3 measurement was preferred instead of L1, L2 and L4 vertebrae to avoid any false results. Neck and total femoral measurements were performed to evaluate the appendicular osteoporosis in all patients. Tibial bone mineral density (g/cm^2) was also measured. For proximal tibial measurement, patients lied in supine position with legs in anatomical position. For proximal tibial images region of interest (ROI) box was placed centrally on proximal tibia and at 15 pixell below the plateau. ROI box dimension was 40x20 pixell (13).

Calcaneal QUS scanning was performed by Hologic-Sahara. Patient's heel was placed in between transducers and the heel width was measured accurately. SOS (speed of sound), BUA (bone ultrasound attenuation) and endurance were evaluated.

In this study, we used the classification of WHO to determine the amount of bone loss (14). Vertebral fracture was determined semi-quantitatively according to Genant (15). Two clinicians evaluated the dorsal and lumbosacral lateral X-rays at two different time periods independently.

The statistical analysis was performed using the program SPSS for Windows 10.0. For mean and standart deviations Students' t test, for parametric analysis, Mann Whitney U tests, for nonparametric analysis chi-Squared test were used. Spearman and Pearson correlation tests were applied where available. Logistic regression analysis was preferred to calculate the effects on osteoporosis (CI %95, $p<0.05$).

Results

Average age of Group 1 was 36,8 years, body mass index was 24.9±4.2 kg/m^2 and duration of disease was 7.6±6.8 years. In Group 2 average age was 37.3 years, BMI was 23.9±4.5 kg/m^2. There wasn't any significant difference between the groups ($p>0.05$). Average L3 (lat) bone mineral density indicated osteopenia and was significantly lower in patients (t: -1.4, versus -0.0009, $p<0.05$) but both of the groups had similar for AP L3 BMD`s (0.81 and 0.92 g/cm^2 respectively, $p>0.05$). There wasn't a significant correlation between BMD and age, BMI or duration of disease neither in patients nor in the control group ($p>0.05$).

With respect to control group, femoral neck (0.91 v.s. 1.03 g/cm^2 respectively p<0.001, t-1.2 v.s. -0.2 p<0.001) and total femoral BMD (0.92 vs. 1.02 g/cm^2 respectively, p<0.001, t-1.2 v.s. -0.2, p<0.001) values were significantly lower in the patients, but there wasn't a significant difference in tibial BMD values (0.70 and 0.76 g/cm^2, p>0.05 respectively) (Table 1).

Calcaneal QUS measurements were only performed in group 1. We found a positive, moderate and statistically significant correlation between heel BUA and stiffness values and total femur BMD (g/cm^2, r: 0.408) (p<0.05). QUS parameters were not correlated with tibial BMD (Table 2).

In both groups there was a positive and statistically significant correlation between femoral neck (g/cm^2, r: 0.643), total femur (g/cm^2, r: 0.698) values and tibial bone content (g/cm^2) (p<0.01) (Table 3).

There was a highly negative correlation between sedimentation rate and L3 BMD (both in terms of g/cm^2 and t values) (r: -0.462 and r: -0.443, p<0.01). Both sedimentation rate and total femur BMD (g/cm2) and CRP and femoral neck BMD (g/cm^2) were significantly and negatively correlated (r: -0.356 p<0.05). Calcium level was highly correlated with femoral neck t score (r: 0.449). ALP was negatively and moderately correlated to femoral neck BMD, total femoral t value and tibial BMD (p<0.05) (Table 4).

Logistic regression analysis revealed the order of effectiveness on osteoporosis as CRP, BASMI, duration of the disease, age and sedimentation rate. CRP increases the risk of development of osteoporosis by 1.72 folds, BASMI 1.38, duration of disease 1.06, age 1.046 and sedimentation rate 1.04 folds. BASFI, BASDAI, BDS and fatigue were not found to be effective on osteoporosis. Femoral neck BMD values were correlated with only physical role difficulty (r: 0.325 p<0.05) (Table 5). Among 8 patients with vertebral fractures on X-rays, 4 of them had normal bone density at L3, 3 had osteopenia and one had osteoporosis. Vertebral fracture was not found to be correlated with osteoporosis (p>0.05).

Discussion

The aim of this study was to determine osteoporosis and related factors in patients with AS and also to observe the effects of bone density on clinical presentation. Osteoporosis and increased fracture risk are frequent complications of AS (1). Spinal osteoporosis may be the result of inactivity but Will et al. (1) reported osteopenia at lumbar spine and femoral neck in early AS with normal spinal movements and physical activity (16,17). Recent studies also showed the relation between bone loss and inflammatory activity in early AS.

Toussirot et al. (18) studied 71 AS patients and 70 healthy controls and reported that 53.5% were normal, 32.4% had osteopenia and 14.1% had osteoporosis.

We found that almost half of our patients had osteopenia (47.7%) and one third had osteoporosis (31.6%). Although there wasn't any relation between vertebral fracture and osteoporosis, 8 patients (21%) had vertebral fractures. Mitra et al. (19) also evaluated 66 men with AS; diagnosed low BMD both on lumbar spine and hip, but these values were also not correlated with vertebral fracture.

Raltson et al. (20) investigated the prevalence of vertebral fracture due to osteoporosis in AS, and found that 16% of 111 patients had compression fracture and 5 patients had biconcave vertebrae. The patients with fracture had decreased spinal mobility and chest expansion with a marked spinal deformity.

Donnelly et al. (21) found vertebral fracture rate as 10.3% and in relation with advanced age, male sex, long duration of disease and decreased spinal mobility. Lumbar BMD values and hence prediction of fracture risk were not reliable due to syndesmophytes.

Bronson et al. (5) reported both spinal and femoral osteopenia in 19 patients and suggested that L3 (lat) projection was a more sensitive determinant of vertebral BMD than anteroposterior position. We also preferred lateral decubitus position to avoid

Table 1. Comparison of DXA results between AS and control groups.

BMD	AS		Control		p
	Mean	SD	Mean	SD	
L3 BMD (g/cm^2)	0.81	0.33	0.92	0.16	0.082
L3 t-score	-1.14	1.92	-0.009	1.29	**0.013***
Femural neck BMD (g/cm^2)	0.91	0.14	1.03	0.12	**0.0001****
Femural neck t score	-1.21	1.13	-0.29	0.92	**0.001***
Femural total BMD (g/cm^2)	0.92	0.14	1.02	0.11	**0.001***
Femural total t score	-1.21	1.14	-0.48	0.90	**0.007****
Tibia BMD (g/cm^2)	0.70	0.31	0.76	0.18	0.288

Table 2. Correlation of QUS with DXA results.

BMD	BUA		SOS		Stiffnes	
	r	p	r	p	r	p
L3 (g/cm^2)	0.148	0.419	0.089	0.627	0.138	0.451
L3 t score	0.120	0.520	0.078	0.677	0.102	0.586
Femoral neck BMD (g/cm^2)	0.336	0.080	0.176	0.369	0.348	0.069
Femoral neck t-score	0.241	0.225	0.143	0.477	0.262	0.187
Total hip BMD (g/cm^2)	0.408	**0.031***	0.257	0.188	0.427	**0.023***
Total hip t-score	0.387	**0.046***	0.237	0.234	0.400	**0.039***

false results. It had the difficulty of standardization of which we compared our results with age and sex matched controls.

Low BMI and low fat mass rate are important for development of osteoporosis (5). We couldn't find any correlation between BMI and bone mineral density in our study.

QUS is an alternative method at peripheral skeleton (22). We used calcaneal QUS in our study to observe the correlation between DXA and QUS. It has been shown that calcaneal BUA has a moderate correlation with the hip and the lumbar spine BMD in populations without AS (23). Toussirot et al. (18) reported a mild to good correlation between lumbar spine, femoral neck and total body BMD and calcaneal QUS values. In our study there was a moderate correlation between calcaneal QUS (BUA and stiffness) values and total hip BMD values as shown in Table 2.

Tibial BMD is a peripheral skeleton measurement and it has not been used in an AS group before. Warden et al. (13) studied 15 men after spinal cord injury and found that calcaneal QUS and tibia BMD were correlated. In our study there was a correlation between tibial and femoral values in AS patients.

In the study of Meirelles et al. (24) 30 patients with AS were divided into two groups with respect to disease activity and found that lumbar spine, total proximal femur, femoral neck, trochanter

Table 3. Correlation between femoral and tibial DXA results.

		Tibia	
		r	p
AS	Femoral neck BMD (g/cm²)	0.643	**0.0001****
	Femoral neck t-score	0.607	**0.0001****
	Total hip BMD (g/cm²)	0.688	**0.0001****
	Total hip t-score	0.648	**0.0001****
Control	Femoral neck BMD (g/cm²)	0.634	**0.0001****
	Femoral neck t-score	0.634	**0.0001****
	Total hip BMD (g/cm²)	0.706	**0.0001****
	Total hip t-score	0.696	**0.0001****

Table 4. Correlations between BMD and laboratory values.

	ESR		CRP		Ca		ALP	
	r	p	r	p	r	p	r	p
L3 BMD (g/cm²)	-0.462	0.004	-0.187	0.289	0.272	0.099	-0.103	0.548
L3 t-score	-0.443	0.007	-0.220	0.218	0.261	0.118	-0.132	0.451
Femoral neck BMD (g/cm²)	-0.242	0.176	-0.356	**0.049***	0.427	**0.012***	-0.334	0.062
Femoral neck t- score	-0.177	0.333	-0.356	0.053	0.449	**0.009****	-0.360	**0.047***
Total hip BMD (g/cm²)	-0.372	**0.033***	-0.309	0.091	0.359	0.037*	-0.318	0.076
Total hip t-score	-0.307	0.088	-0.323	0.082	0.341	0.052	-0.371	**0.040***

Table 5. BMD and quality of life (SF-36).

		Physical function	Physical role difficulty	Pain	General health	Energy	Social function	Emotional role difficulty	Mental health
L3 BMD (g/cm²)	r	0.062	0.028	-0.131	0.120	-0.119	0.020	-0.239	-0.024
	p	0.688	0.857	0.391	0.431	0.437	0.8996	0.114	0.875
L3 t-score	r	0.076	0.021	-0.127	0.108	-0.134	0.002	-0.321	0.030
	p	0.624	0.892	0.412	0.485	0.388	0.990	**0.034***	0.848
Femoral neck BMD (g/cm²)	r	0.275	0.307	0.206	0.178	0.136	-0.116	-0.036	0.009
	p	0.078	**0.048***	0.191	0.260	0.389	0.466	0.821	0.955
Femoral neck t-score	r	0.282	0.325	0.244	0.141	0.135	-0.117	-0.088	0.026
	p	0.074	**0.038***	0.124	0.378	0.400	0.465	0.583	0.871
Total hip BMD (g/cm²)	r	0.288	0.137	0.023	0.230	-0.052	-0.150	-0.150	-0.139
	p	0.064	0.387	0.885	0.143	0.741	0.342	0.342	0.382
Total hip t-score	r	0.290	0.141	0.055	0.191	-0.072	-0.144	-0.200	-0.130
	p	0.066	0.378	0.735	0.230	0.656	0.368	0.211	0.418

major, intertrochanteric region BMD values were similar in two groups but Ward's triangle BMD values were different. Toussirot et al. (18) showed that only duration of disease and femoral neck BMD showed significant correlation. In our study there was a correlation between ESR, lumbar and total hip DXA scores and also between CRP and femoral neck BMD values. The strongest predictor of osteoporosis was CRP which increased the risk of development of osteoporosis by 1.72 folds. Limited mobility of spine (BASMI) increased the risk of osteoporosis by 1.38 folds, but BASDAI did not have an effect.

Bronson et al. (5) investigated BMD and biochemical markers of bone metabolism in AS patients and found mildly elevated ALP levels were in correlation with BMD. In our study, femoral and tibial BMD values were correlated with ALP levels. Vitamin D metabolites are effective on both osteoblasts and osteoclasts. Vitamin D was thought to be an etiological factor due to its effects on bone turnover and studies revealed that disease activity (ESR, CRP, BASDAI) and serum vitamin D levels were negatively correlated. PTH plays a major role in the renal synthesis of vitamin D and there is evidence that the Ca ion itself regulates this process. Supression of 1-α hydroxylase activity due to physiological regulation can be seen due to hypercalcemia and PTH supression. Toussirot et al. (25) showed the relation between ESR and urinary pyridinium crosslinks in AS patients.

Mitra et al. (26) evaluated the relation between sex hormones, BMD values and vertebral fracture in 56 men with AS. He could not find a relation between FSH, LH, total testosterone and free testosterone index and BMD measurements and vertebral fracture. We also could not find any relation between BMD and PTH, LH and testosterone levels.

In addition to disease duration; peripheral arthritis, pelvic arthritis, neck involvement, early onset and comorbidities affect the quality of life. Out of 177 patients with an average age of 43 and 18 years of mean disease duration, 31% had depression and its rate was higher in women (46%) than in men (26%). Depression was related to the severity of pain in women and in men, it was additionally related to functional impairment (27). Fatigue is a major symptom in AS studies. Jones et al (28). reported that pain, stiffness and functional ability were related to the level of fatigue.

To our knowledge this article is one of the firsts that evaluates the relation between quality of life, fatigue and depression and bone mineral density in AS patients. In our study only the SF-36 physical role difficulty subgroup and the femoral neck DXA values (g/cm^2, t-scores) had a positive, significant correlation.

We can conclude that osteoporosis and vertebral fractures were frequent complications of AS and alternative methods, such as calcaneal QUS and tibial BMD measurement may be considered in determining bone density. Vertebral fracture development may be independent of BMD. The role of limitation of spinal mobility was apparent in osteoporosis. Some laboratory parameters of osteoporosis and inflammation like Ca, ALP, ESR and CRP were correlated with BMD. Though depression and fatigue have been reported in previous studies to be related with functional impairement, we could not find any correlation between these two clinical features and BMD in our study.

References

1. Lange U, Jung O, Teichmann J, Neeck G. Relationship between disease activity and serum levels of vitamin D metabolites and parathyroid hormone in ankylosing spondylitis. Osteoporos Int 2001;12:1031-5.
2. Speden DJ, Calin A, Ring JF, Bhalla KA. Bone mineral density, calcaneal ultrasound, and bone turnover markers in women with ankylosing spondylitis. J Rheumatol 2002; 29:516-21.
3. Will R, Bhalla AK, Palmer R, Ring F, Calin A. Osteoporosis in early ankylosing spondylitis: a pathological event. Lancet 1989;2:1483-5.
4. Bessant R, Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? J Rheumatol 2002;29:1511-9.
5. Bronson DW, Walker ES, Hillman SL, Keisler D, Hoyt T, Allen HS. Bone mineral density and biochemical markers of bone metobolism in ankylosing spondylitis. J Rheumatol 1998;25:929-35.
6. Van der Linden S, Van der Heijde. Spondyloarthropathies. In: Kelly, Ruddy S, Harris ED, Sledge CB (ed.). Textbook of Rheumatology. WB Saunders Company, Philadelphia 2001; p. 1039-53.
7. Calin A, Garret 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 Functional Index. J Rheumatol 1994;2:2281-5.
8. Garret S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
9. Jenkins TR, Mallorie PA, Whitelock HC, Kennedy LG, Garret SL, Calin Defining spinal mobility in ankylosing spondylitis. The Bath Ankylosing Spondylitis Metrology Index. J Rheumatol 1994;21:1694-8.
10. Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol 1984;40:1365-7.
11. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995;22:639-43.
12. Ariza-Ariza R, Hernandez-Cruz B, Navarro-Sarabia F. Physical Function and Health Related Quality of Life of Spanish Patients with Ankylosing Spondylitis. Arthritis Rheum 2003;49:483-7.
13. Warden JS, Bennel LK, Matthews B, Brown JD, McMeeken MJ, Wark DJ. Quantitative ultrasound assessment of acute bone loss following spinal cord injury: a longitudinal pilot study. Osteoporos Int 2002;13:586-92.
14. Marcus R. The nature of osteoporosis. Marcus R, Feldman DD, Kelsey J (ed.), Osteoporosis. San Diego, 1996;647-9.
15. Genant HK, Jergas M. Assessment of prevalent and incident vertebral fractures in osteoporosis research. Osteoporos Int 2003;14:43-55.
16. Will R, Palmer R, Elvins D, Ring F, Bhalla AK. A lower femoral neck BMD occurs in patients with ankylosing spondylitis (AS) compared with their normal sex siblings. In: Christiansen C, Overgaard K, editors. Osteoporosis 1990. Denmark: Handelstrykkeriet Aalborg, 1990:1672-4.
17. 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. Arhritis Rheum 1999;42:2319-24.
18. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology 2001;40:882-8.
19. Mitra D, Elvins MD, Speden JD, Collins JA. The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. Rheumatology 2000;39:85-9.
20. Raltson HS, Urquhart KDG, Brzeski M, Sturrock DR. Prevalence of vertebral fractures due to osteoporosis in ankylosing spondylitis. Br Med J 1990;300:563-5.
21. Donnelly S, Doyle VD, Denton A, Rolfe I, McCloskey VE, Spector DT. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. Ann Rheum Dis 1994;53:117-21.
22. Faulkner KG, McClung MR, Coleman LJ, Kingston-Sandahl E. Quantitative ultrasound of the heel: correlation with densitometric measurements at different skeletal sites. Osteoporosis Int 1994;4:42-7.
23. Hans D, Dargent-Molina P, Schott AM, Sebert JL,Cormier C, Kotzki PO, et al. Ultrasonographic heel measurement to predict hip fracture in elderly women: the EPIDOS prospective study. Lancet 1996;348:511-4.
24. Meirelles SE, Borelli A, Camargo PO. Influence of disease activity and chronicity on ankylosing spondylitis bone mass loss. Clin Rheumatol 1999;18:364-8.
25. Toussirot E, Richard-Blum S, Dumoulin G, Cedoz JP, Wendling D. Relationship between urinary pyridinium cross-links, disease activity and disease subsets of ankylosing spondylitis. Rheumatology 1999;38:21-7.
26. Mitra D, Elvins DM, Collins AJ. Testosterone and testosterone free index in mild ankylosing spondylitis: relationship with bone mineral density and vertebral fractures. J Rhematol 1999;26:2414-7.
27. Ward MM. Quality of Life in Patients with Ankylosing Spondylitis. Rheum Dis Clin North Am 1998;24:815-27.
28. Jones SD, Koh WH, Steiner A, Garret SL, Calin A. Fatigue in ankylosing spondylitis: Its prevalence and relationship to disease activity, sleep and other factors. J Rheumatol 1996;23:487-90.