Vertebral Fractures in Ankylosing Spondylitis Are Associated with Lower Bone Mineral Density in Both Central and Peripheral Skeleton

EVA KLINGBERG, MATS GEIJER, JAN GÖTHLIN, DAN MELLSTRÖM, MATTIAS LORENTZON, ELISABET HILME, MARTIN HEDBERG, HANS CARLSTEN, and HELENA FORSBLAD-D'ELIA

ABSTRACT. ***Objective.*** To study the prevalence and risk factors for vertebral fractures (VF) in ankylosing spondylitis (AS) and the relation between VF, measures of disease activity, and bone mineral density (BMD) in different measurement sites.

Methods. Patients with AS (modified New York criteria) underwent examination, answered questionnaires, and gave blood samples. Lateral spine radiographs were scored for VF (Genant score) and syndesmophyte formation through modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). BMD was measured with dual-energy x-ray absorptiometry in the hip, radius, and lumbar spine in anteroposterior and lateral projections with estimation of volumetric BMD (vBMD).

Results. Two hundred four patients (57% men) with a mean age of 50 ± 13 years and disease duration 15 ± 11 years were included. VF were diagnosed in 24 patients (12%), but were previously noted clinically in only 3 of the 24. Patients with VF were significantly older (p = 0.004), had longer disease duration (p = 0.011), higher Bath Ankylosing Spondylitis Metrology Index (p = 0.011), mSASSS (p = 0.035), and Bath Ankylosing Spondylitis patient global score-2 (BASG-2) (p = 0.032) and were more often smokers (p = 0.032). All women with a VF were postmenopausal. BMD was significantly lower at all measuring sites in the patients with VF. In logistic regression, high BASG-2, low BMD in femoral neck, and low lumbar vBMD were independently associated with presence of VF.

Conclusion. VF in AS are common but are often not diagnosed. VF are associated with advanced age, longstanding disease, impaired back mobility, syndesmophyte formation, and lower BMD in both the central and peripheral skeleton. BMD in the femoral neck, total hip, and estimated vBMD showed the strongest association with VF. (J Rheumatol First Release Aug 15 2012; doi:10.3899/jrheum.120316)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SPONDYLOARTHROPATHY OSTEOPOROSIS
VERTEBRAL FRACTURE BONE MINERAL DENSITY
DUAL-ENERGY X-RAY ABSORPTIOMETRY

Ankylosing spondylitis (AS) is a chronic rheumatic disease causing inflammation in the sacroiliac joints, vertebrae, and ligamentous apparatus of the spine. Osteoporosis is a complication of AS that can present in early disease[1,2]. Diagnosing osteoporosis in AS can be difficult, however. The pathological new bone formation around the vertebrae, characteristic for the disease, can cause an overestimation of the bone mineral density (BMD) in the lumbar spine measured with dual energy x-ray absorptiometry (DEXA) in the anteroposterior (AP) projection. Consequently, BMD thus measured can be normal even if vertebral osteoporosis is present[3,4,5,6]. Measuring lumbar BMD in the lateral pro-

From the Department of Rheumatology and Inflammation Research and the Centre for Bone and Arthritis Research, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg; Centre for Medical Imaging and Physiology, Skåne University Hospital, and Lund University, Lund; Department of Radiology, Sahlgrenska University Hospital, Mölndal; Department of Rheumatology, Hospital of Alingsås, Alingsås; and Department of Rheumatology, Hospital of Borås, Borås, Sweden.

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E. Klingberg, MD, Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg; M. Geijer, MD, PhD, Centre for Medical Imaging and Physiology, Skåne University Hospital, Lund University; J. Göthlin, MD, Professor, Department of Radiology, Sahlgrenska University Hospital/Mölndal; D. Mellström, MD, Professor; M. Lorentzon, MD, Associate Professor, Centre for Bone and Arthritis Research, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg; E. Hilme, MD, PhD, Department of Rheumatology, Alingsås; M. Hedberg, MD, Department of Rheumatology, Borås; H. Carlsten, MD, Professor; H. Forsblad-d'Elia, MD, Associate Professor, Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg.

Address correspondence to Dr. E. Klingberg, Department of Rheumatology, Sahlgrenska/SU, Gröna stråket 14, S-413 45 Gothenburg, Sweden. E-mail: Eva.Klingberg@vgregion.se

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jection could be a better method, because lateral scanning includes solely the vertebral bodies in the measurement and excludes the posterior part of the vertebrae. Combining AP and lateral DEXA scans also allows estimation of volumetric BMD (vBMD).

Earlier work has demonstrated a higher risk for vertebral fractures (VF) in patients with AS than in the general population[7,8,9]. Nevertheless, many cases of VF in AS do not come to clinical attention, because symptoms may be absent or misinterpreted as increased disease activity. The fractures can also be difficult to identify with radiography when the spine is affected with advanced ankylosis or osteoporosis. Additionally, the fracture lines can run through parts of the vertebrae that are difficult to visualize on plain radiographs, such as the posterior pedicles or disc spaces. Unlike vertebral compression fractures associated with osteoporosis in old age, spinal fractures in AS can be unstable and complicated with injuries of the spinal cord and nerve roots. The biomechanics of the spine in AS are altered because of the fusion of the vertebrae by syndesmophyte formation and calcification of the ligamentous apparatus. Spinal rigidity in combination with brittle bone quality caused by osteoporosis allows highly unstable fractures to develop after even minor trauma[10,11,12].

Our aims were to (1) study the prevalence of VF in AS; (2) identify demographic and disease-related measures that constitute risk factors for VF; (3) study the relation between VF and BMD measured with DEXA at different sites; and (4) investigate the effect of VF on spine mobility in AS.

MATERIALS AND METHODS

Patients. Patients were enrolled between February and April 2009 from 3 participating centers in western Sweden: the Rheumatology Clinic at Sahlgrenska University Hospital (SU) in Gothenburg and the Rheumatology Clinics at the Borås and Alingsås county hospitals. Only patients meeting the modified New York criteria for AS were included[13]. Exclusion criteria were psoriasis, inflammatory bowel disease, dementia, pregnancy, and difficulties in understanding Swedish. The medical records of all patients with AS registered in the hospitals' databases were reviewed. All patients meeting the study criteria were invited to participate. Patients gave written informed consent according to the Declaration of Helsinki. The study was approved by the regional ethics committee in Gothenburg.

Patients underwent examination by the same physician (EK), including Bath Ankylosing Spondylitis Metrology Index (BASMI), according to the Assessment of Spondyloarthritis international society handbook and 68/66 joint counts for numbers of tender and swollen joints[14,15]. With the patient standing erect, vertebra C7 and 30 cm below was marked for thoracic flexion and C7 to S1 for the Stibor test. The patient then bent forward maximally and the increased distance for the measurements was recorded. The distance from C7 to the wall was measured for the Fleche test.

Patients answered questionnaires concerning risk factors for osteoporosis, medical history, medication, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis patient global score (BAS-G). BAS-G1 is the patient's global score concerning the previous week and BAS-G2 concerns the last 6 months[16,17,18]. Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated using a previously reported formula[19,20].

Physical activity was divided into 3 levels of intensity (light, moderate, and heavy) and reported in hours per week during leisure time, at home, and at work using 2 validated questionnaires: Leisure Time Physical Activity Instrument (LTPAI) and Physical Activity at Home and Work Instrument (PAHWI)[21].

Bone mineral density (BMD) was measured using a DEXA scanner (Hologic Discovery A, Hologic Inc., Bedford, MA, USA) for the lumbar spine in the AP (L1-L4) and lateral (L2-L4) projections, in the nondominant hip (femoral neck, total hip), and in the nondominant forearm.

For patients aged 50 years or older the following World Health Organization (WHO) definition of osteopenia and osteoporosis was used: osteopenia T score < -1 to > -2.5 SD and osteoporosis T score ≤ -2.5 SD[22]. The lowest value of BMD measured in the lumbar spine, total hip, or femoral neck was used. For patients under age 50 years, a Z score ≤ -2.0 was considered to be below the expected range for age and a Z score > -2.0 within the expected range for age. T scores (using BMD values for healthy young women and men) and Z scores (using BMD values for healthy age-matched women and men) were provided by the DEXA scanner software.

Lateral radiographs of the cervical, thoracic, and lumbar spine were acquired. All radiographs were assessed by 2 independent radiologists (JG and MG). VF were scored using the Genant score, a semiquantitative technique evaluating the Th4–L4 vertebrae. The vertebrae were scored on visual inspection as normal (grade 0), mildly deformed (grade 1, 20%–25% reduction of the anterior, middle, or posterior height), moderately deformed (grade 2, 25%–40% reduction in any height), or severely deformed (grade 3, over 40% reduction in any height)[23]. Radiographic changes related to AS in the spine were assessed by the modified Stoke Ankylosing Spondylitis Spine Score, scoring totally 24 anterior corners of the C2-Th1 and Th12-S1 vertebrae with 0–3 points each (0 = normal; 1 = erosion, sclerosis, or squaring; 2 = syndesmophyte formation; 3 = bridging syndesmophyte). Scoring scale range was 0–72[24].

The lifetime use of glucocorticoids, converted into milligrams of prednisolone, was estimated both by examining patients' medical records and by asking patients about previous glucocorticoid injections and oral prednisolone use.

The mean erythrocyte sedimentation rate (ESR) during the previous 5 years was calculated using the first-noted ESR each year. An ESR test was excluded and the next consecutive ESR test was used if the medical records showed that the patient had had an infection at the time of the ESR test.

Laboratory tests. Blood samples were stored at −20ºC until needed for analyses. ESR, C-reactive protein (CRP), hemoglobin (Hb), white blood cell count, platelet count, creatinine, alanine aminotransferase, and ionized calcium were analyzed by standard laboratory techniques.

Statistics. Statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc., IBM, Chicago, IL, USA). Descriptive statistics are presented as median and range and/or mean and SD. The T test was used for comparison of normally distributed demographic and disease-related variables and the Mann-Whitney U test for non-normally distributed variables. The chi-square test was used to compare categorical variables. Correlations were calculated using Spearman's correlation (r_s). In dichotomous variables an event was coded 1 and no event coded 0. All tests were 2-tailed and $p < 0.05$ was considered statistically significant. Multiple linear regressions were run with continuous variables as outcome and logistic regression with categorical variables as outcome.

RESULTS

Enrollment of patients and the procedure of the trial is shown in Figure 1.

The patients who fulfilled inclusion criteria but declined participation or did not respond to an invitation were significantly younger than the included patients (46 ± 13 vs 50 ± 13 yrs; $p = 0.007$), but the sex distribution was not significantly different between included and not included patients (57% men vs 66% men; $p = 0.10$).

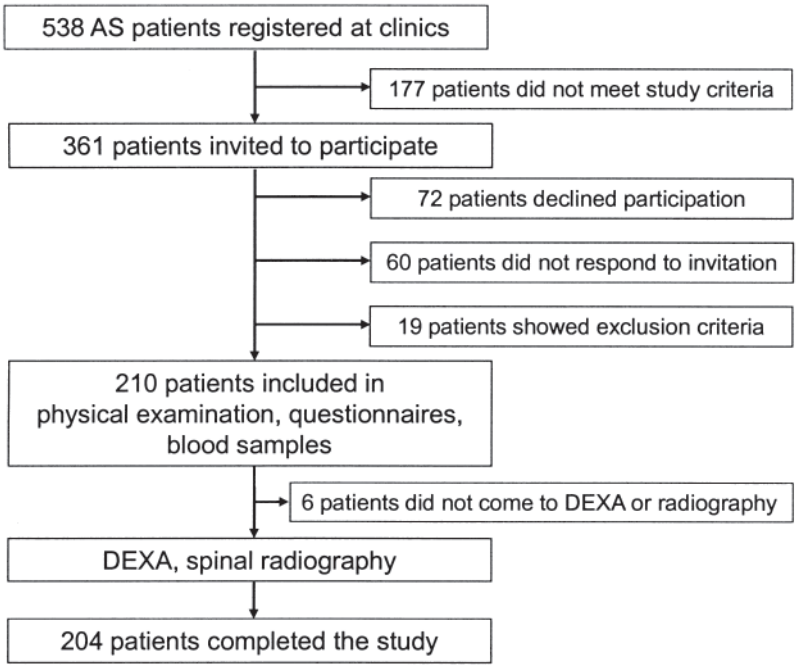

Figure 1. Procedure of the trial, and description of patients who did not complete the study or were excluded. AS: ankylosing spondylitis; DXA (DEXA): dual-energy x-ray absorptiometry.

A total of 204 patients completed the study: 117 men (57%) and 87 women (43%). Age (mean ± SD, 50 ± 13 yrs), time since onset of AS symptoms (24 ± 13 yrs), and time since diagnosis (15 ± 11 yrs) were evenly distributed between the sexes. Men had a significantly higher mSASSS score (median 8, range 0–72) compared to women (median 2, range 0–46; $p < 0.001$). BAS-G2 was significantly higher in women (median 4.1, range 0.2–9.7) than in men (median 2.6, range 0–9.6; $p = 0.04$). There were no significant differences in BASDAI, ASDAS, BAS-G1, BASFI, or BASMI scores between women and men. Demographic and disease-related variables are given in Table 1.

In patients age 50 years or older (n = 101), osteopenia was found in 44 (43.6%) and osteoporosis in 21 (20.8%), using the WHO definition[22]. In patients under age 50 years (n = 103), BMD below the expected range for age was found in 5 patients (4.9%).

Prevalence of VF. Lateral radiographs were evaluated for the Genant score (Th4-L4) in all patients. A total of 42 VF were found by radiography (Th4-L4) in 24 patients (11.8%). The fractures were most frequently localized in the lumbar spine (n = 25) followed by the thoracic spine (n = 17; Figure 2). One patient had 4 fractures, 4 patients had 3 fractures, and 7 patients had 2 fractures. Of 19 patients age 50 years or more with VF, 8 had osteoporosis and 6 had osteopenia according to the WHO definition. Five patients with VF were younger than 50 years and 1 of them had a Z score below the expected range for age. Three patients reported knowledge of having a VF. Thus, 21 patients had 1 or more previously undiagnosed VF. Although the cervical spine is not included in the Genant score, it was in our study assessed for VF, and 5 cervical fractures in 3 patients were found. However, only the vertebrae in the Genant score were used in further statistical analyses.

The prevalence of VF and the Genant score were evenly distributed over the women and men, but the men with VF were significantly younger than the women with fractures (53.2 ± 10.2 vs 63.4 ± 5.8 yrs; $p = 0.012$). All patients who were diagnosed with a VF before age 50 years were male. Three patients were diagnosed with VF within the first 10 years after onset of AS symptom, the youngest being 31 years old.

In 56 patients (27.5%), there were no AS-related changes in the cervical or lumbar spine (mSASSS = 0) and their maximum BASMI score was 4.0. The prevalence of VF (2 patients) among the patients with mSASSS score 0 was significantly lower compared to patients with radiographic AS changes ($p = 0.025$). There were significantly more women (70%; $p < 0.001$) in the group of patients with no AS changes in cervical or lumbar spine and the mean age and symptom duration was significantly lower.

Prevalence of peripheral fractures. Eighteen patients (11.3%) reported having had a total of 22 clinical peripheral fractures, evenly distributed in patients with and those without VF. The locations were 7 wrist, 4 arm, 3 foot or ankle, 2 elbow, 2 rib, 1 hip, 1 leg, 1 clavicle, and 1 hand.

Table 1. Characteristics of 204 patients with ankylosing spondylitis in western Sweden.

Characteristic	n (%)	Median (range)	Mean ± SD
Demographic variables			
Sex			
Women	87 (43)		
Men	117 (57)		
Postmenopausal women	45		
Age, yrs		49 (17, 78)	50 ± 13
Heredity for fractures	57 (28)		
Current smokers	24 (12)		
Ever smokers (> 6 months)	101 (49.5)		
Daily calcium intake, dairy products, mg/day		600 (0, 2640)	668 ± 397
BMI		25 (19, 46)	26 ± 4
LTPAI total, hours per week		6 (0, 42)	7.5 ± 6
Disease-related variables			
Yrs since onset of symptoms		24 (2, 55)	24 ± 13
Yrs since diagnosis		12 (1, 47)	15 ± 11
History of anterior uveitis	102 (50)		
History of peripheral arthritis	120 (59)		
History of coxitis	17 (8)		
BASMI, score		3.0 (0.6, 7.4)	3.1 ± 1.6
BASDAI, score		3.5 (0, 9.6)	36 ± 2.1
BASFI, score		2.3 (0, 8.7)	2.7 ± 2.1
BAS-G1, score		2.9 (0, 10)	3.4 ± 2.6
BAS-G2, score		3.4 (0, 9.7)	3.8 ± 2.6
ASDAS, score		2.3 (0.8, 5.9)	2.4 ± 0.9
mSASSS, score		5.5 (0, 72)	14.2 ± 19.2
ESR, mm/h		11 (2, 105)	15 ± 14
Mean ESR 2004–2008, mm/h		16 (2, 102)	19 ± 15
CRP, mg/l		5 (3, 80)	9 ± 10
Hemoglobin, g/l		139 (105, 166)	139 ± 13
White blood cell count, × 10^9/l		6.7 (2.7, 18.1)	7.0 ± 2.1
Platelets, × 10^9/l		287 (133, 506)	299 ± 75
Creatinine, μmol/l		70 (43, 148)	71 ± 15
HLA-B27-positive	178 (87)		
Patients on NSAID	158 (77)		
Patients on DMARD monotherapy	30 (15)		
Patients on TNF inhibitor monotherapy	10 (5)		
Patients taking DMARD and TNF inhibitor combination therapy	32 (16)		
Patients taking glucocorticoids	7 (3)		
Prednisolone lifetime use, mg		100 (0, 56390)	1397± 5775

BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BAS-G: Bath Ankylosing Spondylitis patient global score; ASDAS: Ankylosing Spondylitis Disease Activity Score; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor; BMI: body mass index; LTPAI: Leisure Time Physical Activity Instrument.

Peripheral fractures were most strongly correlated with lumbar vBMD ($r_S = 0.248$, $p < 0.001$), followed by lateral lumbar BMD ($r_S = 0.238$, $p = 0.001$), AP lumbar BMD ($r_S = 0.214$, $p = 0.002$), BMD total radius ($r_S = 0.173$, $p = 0.014$), and BMD in the femoral neck ($r_S = 0.163$, $p = 0.020$).

Demographic and disease-related variables. The demographic and disease-related variables in Table 1 were explored for association with the categorical variable VF (yes/no).

The presence of a VF correlated significantly with older age, longer disease duration, persistent smoking, and higher BASMI, BAS-G2 and mSASSS scores. All women with a VF were in menopause. The variables that showed significant difference between patients with and those without a VF are given in Table 2. The prevalence of VF in different age groups is shown in Table 3.

There was no significant difference between categories of patients with and those without a VF regarding AS man-

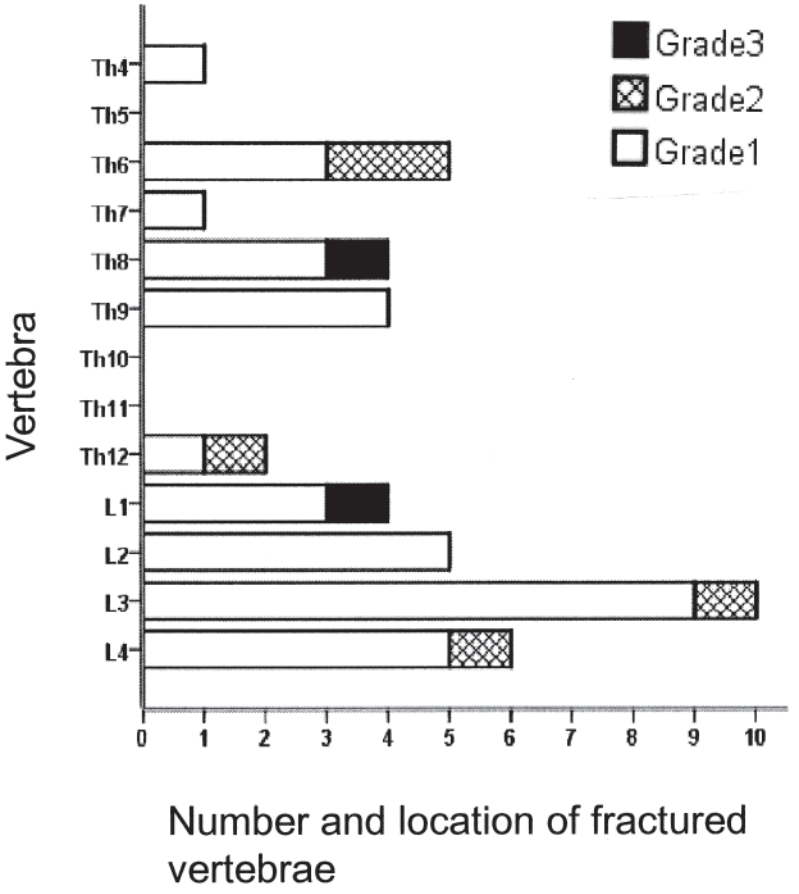

Figure 2. Location of vertebral fractures and grade according to Genant score. Th: thoracic; L: lumbar.

ifestations (peripheral arthritis, coxitis, anterior uveitis, HLA-B27 status, BASDAI, ASDAS, BAS-G1, BASFI), inflammatory measures (ESR, CRP, mean ESR period 2004-2008, Hb), antirheumatic treatment [nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs (DMARD), tumor necrosis factor (TNF) inhibitors, lifetime prednisone use], body mass index, physical activity (LTPAI/PAHWI), or intake of calcium or alcohol.

BMD at different measurement sites. Patients with VF had significantly lower BMD at all measurement sites, compared to patients without a VF (Table 2). The greatest difference in BMD between patients with and those without a VF was found in the femoral neck, followed by lumbar vBMD and BMD in the total hip.

Spearman correlations were also run between the Genant score and BMD from different measurement sites. BMD measured in the femoral neck showed the best correlation with the Genant score ($r_S = -0.262$, $p < 0.001$), followed by BMD in total hip ($r_S = -0.253$, $p < 0.001$), lumbar vBMD ($r_S = -0.231$, $p = 0.001$), lateral lumbar BMD ($r_S = -0.200$, $p = 0.004$), and BMD total radius ($r_S = -0.190$, $p = 0.007$). Lumbar BMD in the normal AP projection showed the weakest association with the Genant score ($r_S = -0.167$, $p = 0.017$).

To analyze BMD as a risk factor for VF in different stages of ankylosis, the span of the mSASSS score (0–72) was divided into 3 parts and the patients were designated accordingly into groups defined as having low-grade changes (mSASSS 0–24, n = 161), intermediate changes (mSASSS 25–48, n = 24), and advanced changes (mSASSS 49–72, n = 18). In the group with low-grade changes, the Genant score correlated significantly with lateral lumbar BMD, lumbar vBMD, and BMD in the total hip and femoral neck. In the group with intermediate changes, significant correlation between BMD and the Genant score could be found only in the total hip ($r_S = -0.575$, $p = 0.003$) and femoral neck ($r_S = -0.540$, $p = 0.006$). In the group with advanced ankylosis, which contained men only, significant correlation between BMD and VF was found in the femoral neck alone ($r_S = -0.542$, $p = 0.020$).

Logistic regression with a forward stepwise conditional method was run with the presence of a VF as binary outcome. BMD and the demographic and disease-related variables significantly correlated with VF were entered as covariates. In the first model, BMD from all measurement

Table 2. Variables showing significant differences between groups of patients with and without at least 1 vertebral fracture.

Variable	Patients with AS with Vertebral Fracture, median (range)/ mean ± SD/n (%)	Patients with AS without Vertebral Fracture, median (range)/ mean ± SD/n (%)	Significance, 2-tailed, p
Age, yrs	58 (31, 74)	49 (17, 78)	0.004
Symptom duration, yrs	29 (9, 51)	22 (2, 52)	0.046
Duration since diagnosis, yrs	20 (2, 40)	11 (1, 47)	0.011
Women in menopause	9/9 (100)	36/78 (46)	0.003
Ongoing smoking	6/24 (25)	18/162 (10)	0.032
mSASSS, score	11.5 (0, 70)	4.5 (0, 72)	0.035
BAS-G2, score	4.7 (0.8, 9.7)	3.0 (0, 9.6)	0.032
BASMI, score	3.8 (1.4, 7.0)	2.8 (0.6, 7.4)	0.011
Stibor test	6.2 (1.5, 9.5)	7.2 (0, 13.5)	0.036
Fleche test	5.0 (2.0, 12.0)	4.0 (0, 16.0)	0.011
Cervical rotation	60 (7.5, 82.5)	65 (0.0, 100.0)	0.05
Thoracic flexion	1.2 (0.0, 3.5)	2.0 (0.0, 6.0)	0.006
Chest expansion	5.0 (2.5, 8.0)	6.0 (3.0, 11.0)	0.016
Schober	3.2 (0.5, 6.0)	4.0 (0.0, 7.0)	0.008
AP lumbar BMD, g/cxm^2	0.943 ± 0.146	1.034 ± 0.173	0.015
Lateral lumbar BMD, g/cm^2	0.646 ± 0.145	0.736 ± 0.131	0.002
Lumbar vBMD, g/cm^3	0.169 ± 0.037	0.195 ± 0.031	< 0.001
Femoral neck BMD, g/cm^2	0.693 ± 0.123	0.797 ± 0.127	< 0.001
Total hip BMD, g/cm^2	0.845 ± 0.130	0.951 ± 0.138	0.001
Total radius BMD, g/cm^2	0.567 ± 0.083	0.611 ± 0.078	0.012

AS: ankylosing spondylitis; BASMI: Bath Ankylosing Spondylitis Metrology Index; BAS-G2: Bath Ankylosing Spondylitis patient global score (6 months); mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; BMD: bone mineral density (areal); AP: anteroposterior; vBMD: volumetric bone mineral density.

Table 3. Prevalence of vertebral fractures in patients with ankylosing spondylitis of different ages.

Age, yrs	Patients with Vertebral Fractures, n (%) in Age Group	Total No. Vertebral Fractures within Age Group
17–29 (n = 10)	0 (0)	0
30–39 (n = 36)	1 (2.8)	1
40–49 (n = 57)	4 (7.0)	4
50–59 (n = 43)	8 (18.6)	12
60–69 (n = 48)	9 (18.8)	20
70–79 (n = 10)	2 (20)	5
All ages (n = 204)	24 (12)	42

sites was entered together with significant demographic and disease-related variables (age, symptom duration, ongoing smoking yes/no, BAS-G2, BASMI, mSASSS, and menopause yes/no). In this model, BAS-G2 (B = 0.20, p = 0.025, OR 1.22, 95% CI 1.02–1.46), BMD femoral neck (B = –4.67, p = 0.051, OR 0.009, 95% CI 8.72 E^{-5}–0.47), and lumbar vBMD (B = –17.86, p = 0.041, OR 1.75 E^{-8}, 95% CI 6.53 E^{-16} –0.47) remained as covariates. A receiver-operating characteristic (ROC) curve was created with VF yes/no as state variable and the results from the logistic regression as test variable (0.20 × BASG2 – 4.67 × BMD femoral neck – 17.86 × lumbar vBMD). The area under the curve was 0.768, with 95% CI 0.66–0.88. In the second model, only BMD femoral neck and AP lumbar spine were entered, together with the same demographic and disease-related variables as in the first model. In this second model, age (B = 0.042, p = 0.054, OR 1.04, 95% CI 0.99–1.09), BAS-G2 (B = 0.20, p = 0.027, OR 1.22, 95% CI 1.02–1.46), and femoral neck BMD (B = –6.41, p = 0.004, OR 0.002, 95% CI 0.00–0.12) remained as covariates. The ROC curve from the second model had an area under the curve of 0.770 (95% CI 0.66–0.88).

VF and back mobility. The Mann-Whitney U tests showed that patients with a VF had significantly longer Fleche test (p = 0.011), poorer cervical rotation (p = 0.05), lower thoracic flexion (p = 0.006), lower modified Schober test (p = 0.008), lower Stibor test (p = 0.036), poorer chest expansion (p = 0.016), and higher BASMI (p = 0.011) compared with patients without a VF (Table 2). Multiple linear regression showed that the Genant score (B = 0.255, p = 0.021) and mSASSS (B = 0.061, p < 0.001) were both independent covariates for BASMI (R^2 = 0.593). Adding age to the linear regression model, mSASSS (B = 0.052, p < 0.001) and age (B = 0.039, p < 0.001) were significant covariates for BASMI (R^2 = 0.593), but the Genant score did not remain as a significant covariate.

DISCUSSION

Our study shows that VF are common in AS and that these fractures often go undiagnosed. VF (Th4-L4) were found in 24 patients (12%), but had previously come to clinical attention in only 3 patients. We also demonstrate that osteoporosis and osteopenia are frequent in patients with AS. In patients aged 50 years or more, osteoporosis according to the WHO definition was diagnosed in 21% and osteopenia in 44%. In patients younger than 50 years, BMD below the expected range for age was found in 5%. In addition, VF were diagnosed in patients with early disease within the first 10 years after onset of symptoms and in patients without radiographic AS changes in the cervical or lumbar spine. The study patients were representative for the patients with AS treated at rheumatology clinics in western Sweden, having a relatively high occurrence of peripheral arthritis (59%) and anterior uveitis (50%) in their medical history and need for treatment with DMARD (30%) and TNF inhibitors (21%).

The proportion of VF that had come to clinical attention in our study (12.5%) was lower than what is estimated in the general population in Sweden, where about 22% of VF in women and 42% of VF in men come to clinical attention[25]. The underdiagnosing of VF and osteoporosis in AS can have serious health consequences. There is multiple evidence of increased mortality following fractures related to osteoporosis[26,27]. A prevalent VF is also a strong predictor for a new fracture. The risk for a new VF within 1 year has been shown to be as high as 20%[28]. In AS it is of particular importance to prevent VF, because fractures can be complicated with neurological injuries.

The prevalence of VF that we found in relation to findings in earlier studies is presented in Table 4. In our study the prevalence of VF was slightly lower compared with other studies, despite higher mean age of the included patients. Additionally, our study has a larger number of patients and a larger percentage of women. The differences in prevalence of VF between the studies could depend on factors such as varying recruitment methods and definitions of a VF, making a straightforward comparison between studies impossible. In contrast to other studies in which fractures were predominantly diagnosed in the thoracic spine, we found the lumbar spine to be the most common location for fractures[29,30,31]. The location of VF was not significantly different between the sexes.

Our study shows that VF should in particular be expected in older patients who smoke, and in patients with long disease duration, impaired back mobility, advanced ankylosis, and poor self-estimated general health. Menopause was shown to be a strong risk factor for women. The relationship between VF and older age, long disease duration, high BASMI, and syndesmophyte formation found in this study is in accord with findings in others[6,9,32]. In a recent study of 3014 elderly Swedish men from the MrOS cohort, low BMD and poor self-estimated general health were found to be independently associated with increased mortality[33]. We found that low BMD and poor self-estimated general health were independently associated with VF.

Other studies have demonstrated that the risk for VF and osteoporosis is increased in male patients with AS[34]. Our results point in the same direction. Although we found no significant difference in prevalence of VF, osteoporosis, or osteopenia between the women with AS and the men, VF appeared at a younger age in the men. All the women who were diagnosed with a VF were in menopause, thus postmenopausal bone loss most likely played an important role

Table 4. The prevalence of vertebral fractures (VF) reported in other studies.

Study	Year	Country	No. Patients	Men (%)	Diagnosis	Age, yrs	Disease Duration, yrs	Prevalence of VF (%)	Definition of VF
Ralston[32]	1990	UK	111	88	SpA	median 41	median 17	21	#1, Th Ha/Hp < 0.80 L Ha/Hp < 0.85
Cooper[7]	1994	USA	158	77	AS*	mean 34	no data	11	#2, radiologists' interpretation
Donelly[6]	1994	UK	87	71	SpA	mean 44	mean 16	9	#1, McCloskey[38]
Sivri[39]	1996	Turkey	22	91	AS*	mean 37	mean 10	41	#1, Ha, Hp < 0.85
Mitra[1]	2000	UK	66	100	AS*	median 38	median 10	17	#1, McCloskey
Lange[4]	2005	Germany	84	63	AS*	mean 32–56, 4 groups	mean 9–32, 4 groups	11	#1, no data
Jun[9]	2006	South Korea	68	100	AS*	mean 31	mean 7	16	#1, no data
Vosse[30]	2006	Netherlands	135	67	AS*	mean 50	mean 9	31	#1, Ha/Hp ≤ 0.80
Ghozlani[29]	2009	Morocco	80	84	AS*	mean 39	mean 11	42	#1, Genant[23] VFA
Mermerci Baskan[31]	2010	Turkey	100	75	AS*	mean 40	mean 11	19	#1, Any height ≤ 0.85
Klingberg		Sweden	204	57	AS*	mean 50	mean 15	12	#1, Genant

* AS fulfilling the modified New York criteria. #1: Morphometric vertebral fractures on radiographs when examining all study patients. #2: Clinical fractures including only fractures that have come to clinical attention and are found in medical registers. AS: ankylosing spondylitis; SpA: spondyloarthritis; Th: thoracic; L: lumbar; Ha/Hp: anterior/posterior vertebral height; VFA: vertebral fracture assessment using dual-energy x-ray absorptiometry.

in the pathogenesis. Our results can also be compared with incidence of VF in women and men found in the European Prospective Osteoporosis Study, in which the incidence of VF was 10.7/1000 per year in European women and 5.7/1000 per year in men and where the occurrence of VF was found to be higher in Sweden than elsewhere in Europe[35].

We show that VF in AS are associated with lower BMD in both the central and the peripheral skeleton. A correlation between VF and BMD has been difficult to show in many studies possibly because of a smaller number of patients[1,6]. In contrast to some earlier studies showing that osteoporosis in AS mainly is located in the central skeleton, we found a high frequency of peripheral osteoporosis[32,36]. Osteoporosis and osteopenia in the distal radius were equally prevalent among men and women. The strongest correlations between the Genant score and BMD were found in the hip (femoral neck and total hip), followed by volumetric lumbar BMD and lateral lumbar BMD. We found persistent association between hip BMD and VF when we looked at subgroups with intermediate and advanced AS changes in the cervical and lumbar spine. An association between hip BMD and VF has been demonstrated in other studies and it has been recommended to use hip BMD as a risk predictor for fractures in advanced AS[9,37]. Our results are in accord with this recommendation.

Volumetric lumbar BMD and lateral lumbar BMD showed stronger correlation with both vertebral and peripheral fractures than AP BMD. These results indicate that volumetric lumbar BMD and lateral lumbar BMD are better predictors for fractures than AP lumbar BMD. However, at present lateral lumbar DEXA is not a valid method to diagnose osteoporosis, but it may be used for followup of osteoporosis treatment.

In our study, VF were associated with significantly poorer back mobility in the cervical, thoracic, and lumbar spine. Syndesmophyte formation using radiographs evaluated with the mSASSS score was an independent covariate for BASMI. However, in statistical analyses we could not show that VF, independent of age, adds to the impairment of back mobility and hyperkyphosis caused by ankylosis in AS. Age is a confounder, because the risks of VF, ankylosis, and spinal rigidity all increase with advancing age. Vosse, *et al* have previously shown that wedging of thoracic vertebrae caused by fractures, together with mSASSS, is an independent risk factor for increased occiput-to-wall distance in patients with AS, even after adjustment for age[30].

VF are common but often undiagnosed in patients with AS in western Sweden and should be suspected particularly in older patients who smoke and patients who have long-standing disease, impaired back mobility, and advanced ankylosis. VF appear at a younger age in men than in women. VF are associated with lower BMD in both the peripheral and the central skeleton. Comparing BMD measurements from DEXA in different sites, BMD of the hip displayed the strongest correlation with VF, followed by volumetric lumbar BMD and lateral lumbar BMD.

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