Rheumatology 2000;39:85–89

The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density

D. Mitra, D. M. Elvins, D. J. Speden and A. J. Collins

Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL, UK

Abstract

Objective. To determine bone mineral density (BMD) in patients with mild ankylosing spondylitis (AS), to establish the prevalence of vertebral fractures and fracture risk in these patients, and to determine the relationship between BMD and vertebral fractures.

Methods. Sixty-six men with mild AS were studied. BMD of the lumbar spine and femoral neck was measured by dual X-ray absorptiometry (DXA) and radiographs of the thoracic and lumbar spine were obtained in all subjects. From the radiographs, vertebral fractures were characterized by a morphometric technique using established criteria. Thirty-nine healthy male subjects aged 50–60 yr, recruited from primary care registers, had spinal radiographs performed and served as controls for vertebral fractures.

Results. In patients with AS, BMD was reduced in both the lumbar spine 0.97 (0.1) g/cm^2 [T score -1.10 (1.3), 95% confidence interval (CI) -0.50, $+0.14$] and femoral neck 0.82 (0.1) g/cm^2 [T score -1.40 (1.2), 95% CI -0.51, $+0.09$]. There was no correlation between BMD of either the lumbar spine or femoral neck and duration of disease in patients with AS. Eleven of 66 (16.7%) patients with AS had a vertebral fracture, compared with one of 39 (2.6%) controls; odds ratio 5.92 (95% CI 1.4, 23.8). AS patients with fractures were not significantly older (mean age 41.4 *vs* 37.8 yr, $P = 0.17$), but had significantly longer disease duration (12.4 *vs* 9.3 yr, $P < 0.05$) than patients without fractures. No significant difference was found in the visual analogue scores for pain in AS patients with fractures compared with those without. No significant correlation was observed between BMD of the lumbar spine or femoral neck and vertebral fractures in patients with AS. In addition, there was no significant difference in the lumbar spine or femoral neck BMD in AS patients with fractures compared with those without.

Conclusions. Spinal and hip osteopenia and vertebral fractures are a feature of mild AS. However, there was no correlation between BMD and vertebral fractures in these patients. AS patients with mild disease had a higher risk of fractures compared with the normal population and this increased with the duration of disease.

KEY WORDS: Mild ankylosing spondylitis, BMD, Spine, Fractures.

Vertebral osteoporosis and fractures are features of advanced ankylosing spondylitis (AS). The occurrence of fractures has been previously thought to be due to mechanical factors in a rigid spine or disuse osteoporosis. Although osteoporosis is common in AS, the prevalence of spinal fractures is more uncertain, with both low [1–4] and high [5–8] levels having been recorded. This is in part related to differences in the patient groups studied. Osteoporosis in patients with early AS has been recorded using dual photon absorptiometers and dual X-ray absorptiometry (DXA) [9–12].

Submitted 25 May 1999; revised version accepted 8 September 1999.

Correspondence to: D. Mitra, 4221 Penn Avenue, Suite 500, Pittsburgh, PA 15224, USA.

Bone mineral density (BMD) is a good determinant of vertebral fractures in women with post-menopausal osteoporosis [13, 14], yet the only study to examine the relationship between BMD and vertebral fractures in AS found no correlation between the two entities [8]. However, the subjects in that study [8] consisted of a mixed population with advanced spinal changes. There are no data concerning the occurrence of vertebral fractures or the relationship between BMD and vertebral fractures in patients with mild AS. This study was therefore carried out to determine the BMD of the lumbar spine and femoral neck in mild AS, to establish the prevalence of vertebral fractures and fracture risk in mild AS compared with control subjects, and to determine the relationship between BMD and vertebral fractures.

© 2000 British Society for Rheumatology

Methods

Subjects

Sixty-six patients with primary AS were recruited consecutively from the out-patient clinics of the Royal National Hospital for Rheumatic Diseases. They consisted of males aged between 20 and 55 yr with primary AS, based on the modified New York criteria [15]. All patients met criteria for mild disease which included a mobile lumbar spine (modified Schober's test ≥ 5 cm), radiographically normal hips, and absent or incipient syndesmophytes in the thoracolumbar spine with a radiological score of ≤ 1 by the criteria of Taylor *et al.* [16]. The control group comprised 39 healthy male subjects, aged 50–60 yr, recruited from primary care registers. These individuals had thoracolumbar radiographs taken previously for a screening survey of osteoporosis [17] and were used as controls for comparison of fracture prevalence. Patients with seronegative spondyloarthropathies other than primary AS and those with secondary causes of osteoporosis were excluded. No patient was on medication known to affect calcium metabolism. Specifically, no patient was on steroids or disease-modifying agents. All patients underwent a detailed clinical assessment. This included details about the history of trauma and the reported duration of early morning stiffness. Patients completed visual analogue scales for pain in the cervical, thoracic and lumbar spine. Peripheral joints were examined for evidence of synovitis and restricted movement. Metrological assessment of each patient was performed using standard techniques. This included modified Schober's test, tragus to wall distance, chest expansion and intermalleolar distance. Radiographs of the spine (anteroposterior and lateral views) and BMD of the lumbar spine and femoral neck were performed in all AS patients within 3 months of each other.

BMD and vertebral morphometry

Measurements of BMD of the lumbar spine (L1–L4) and femoral neck were carried out using a Hologic QDR 1000 (Hologic Inc., Waltham, MA, USA). The results were expressed as g/cm^2 and the number of standard deviations (S.D.) based on a comparison with peak bone mass (T score). The precision error for the lumbar spine was 1.4% and that for the femoral neck was 2.9%. For BMD measurements of the lumbar spine, care was taken to exclude architecturally deformed vertebrae from the analysis. BMD measurements were performed on all sites of the hip. However, measurements of the femoral neck were considered for the analyses in preference to other sites, as the precision of this site was greater than that of the Ward's triangle or the trochanteric sites. In addition, researchers [13] have shown that femoral neck BMD has similar diagnostic accuracy in the prediction of hip fractures as other sites. To determine vertebral fractures all radiographs were evaluated morphometrically. Using a translucent digitizer and cursor, six points were marked on each vertebral body from T4 to L4 to describe the vertebral shape [18]. These six points correspond to the four corners of the vertebral body and the mid-points of the end plates. From these points, anterior (H_a), middle (H_m) and posterior (H_p) heights were determined for each vertebral body using semi-quantitative techniques. Using these heights, the vertebral fractures in the patients and control subjects were characterized using the method described by McCloskey *et al.* [19]. In this method, a predicted posterior height (H_{pred}) is calculated for each vertebra from the posterior heights of up to four adjacent vertebrae. Vertebral deformity is said to be present if any of the following criteria are met:

(1) H_a/H_p decreased and $H_a/H_{pred} < 3$ S.D. below the reference mean;

(2) H_m/H_p decreased and $H_m/H_{pred} < 3$ S.D. below the reference mean; or

(3) H_a/H_{pred} decreased and $H_p/H_{pred} < 3$ S.D. below the reference mean.

Based on the above criteria, three types of vertebral fractures were defined: wedge, biconcave and crush.

Statistical analysis

The prevalence of fractures was calculated based on the number of individuals with at least one vertebral deformity. Mann–Whitney tests were used to compare age, disease duration and BMD in patients with AS with and without fractures. Logistic regression analysis was used to determine the risk of fractures in the patients with AS compared with controls and the results were expressed as odds ratio and 95% confidence intervals (CI). Spearman's correlation was used to determine the association between BMD, disease duration and vertebral fractures. P values less than 0.05 were considered to be statistically significant. The statistical analysis was performed using SPSS/PC.

Results

Baseline descriptive characteristics of patients with AS are described in Table 1. BMD measurements of the lumbar spine and hip are shown in Table 2. Patients with AS had reduced BMD in their lumbar spine and femoral neck. The spread of T scores of the lumbar spine and femoral neck is shown in Fig. 1. There was no correlation between BMD of the lumbar spine or femoral neck and duration of disease in patients with AS. Eleven of 66 (16.7%) patients with AS had a vertebral fracture, compared with one of 39 (2.6%) controls; odds ratio 5.92 (95% CI 1.4, 23.8). Patients with AS with fractures were not significantly older (mean age 41.4 *vs* 37.8 yr, $P = 0.17$), but had significantly longer disease duration (12.4 *vs* 9.3 yr, $P < 0.05$) than patients without fractures. No significant difference was found in the visual analogue scores for pain in AS patients with fractures compared with those without. No significant correlation was observed between BMD of the lumbar spine or femoral neck and vertebral fractures in patients with AS. In addition, there was no significant difference in the lumbar spine or femoral

TABLE 1. Demographic, clinical and radiographic features of patients with mild AS ($n = 66$)

Variable	Median	Range
Age (yr)	37.75	(20–52)
Duration (yr)	9.85	(1–22)
Body mass index	24.98	(18.72–32.91)
VAS cervical spine (0–10 cm)	3.00	(0–8.5)
VAS thoracic spine (0–10 cm)	1.84	(0–8)
VAS lumbar spine (0–10 cm)	3.80	(0–8.7)
Early morning stiffness (min)	60	(0–120)
Tragus wall (cm)	9.85	(7–22.5)
Chest expansion (cm)	4.75	(1–8.5)
Modified Schober's (cm)	7.50	(5–10)
Intermalleolar distance (cm)	115.00	(76–148)
X-ray sacroiliac joint right	3.00	(1–4)
X-ray sacroiliac joint left	3.00	(1–4)
X-ray lumbar spine	1.00	(0–1)
X-ray thoracic spine	1.00	(0–1)
X-ray cervical spine	1.00	(0–3)
X-ray right hip	0.00	(0–1)
X-ray left hip	0.00	(0–1)

Body mass index = [weight (kg)/height (m^2)]; VAS, visual analogue scale.

Sacroiliac joint range (1–4) = possible range.

Cervical, thoracic and lumbar spine range, per criteria of Taylor *et al.* [16].

Hip joint range = observed range.

TABLE 2. BMD measurements of the lumbar spine and hip in patients with AS

Variable	Mean	S.D.	95% CI
BMD (g/cm^2)			
Lumbar spine (L1–4)	0.97	0.14	0.02, 0.06
Femoral neck	0.82	0.12	0.86, 0.8
Femur–trochanter	0.72	0.11	0.74, 0.69
Femur–intertrochanteric area	1.09	0.16	1.1, 1.05
Femur–Ward's triangle	0.77	0.15	0.71, 0.63
Femur–total	0.95	0.13	0.98, 0.91
T score			
Lumbar spine (L1–4)	−1.1	1.3	−0.5, 0.14
Femoral neck	−1.4	1.2	−0.51, 0.09
Femur–trochanter	−0.7	0.98	−0.44, 0.96
Femur–intertrochanteric area	−1	1.07	−0.71, 1.2
Femur–Ward's triangle	−1.31	1.24	−0.98, 1.6
Femur–total	−0.97	1.02	−0.69, 1.2

neck BMD in AS patients with fractures compared with those without.

Discussion

This study demonstrated a reduction of BMD in the lumbar spine as well as the femoral neck and an increased prevalence of vertebral fractures in patients with AS who had mild disease. However, there was no correlation between BMD and vertebral fractures in these patients. The reduced BMD confirms findings of previous studies [9–12]. All the patients in this study had mild disease and care was taken to ensure the absence of advanced changes in their hips and spines. Specifically, all patients had a mobile lumbar spine (modified Schober's test ≥ 5 cm), absent or incipient syndesmophytes in the thoracic and lumbar spine, and normal hip joints. Since the patients in this study did not have advanced changes in their spine, it is unlikely that spinal immobility was an important factor in the pathogenesis of osteoporosis. Pain and stiffness in the spine can reduce mobility. However, it has been shown that patients with AS often exercise more than normal subjects and therefore are unlikely to have disuse osteoporosis [9]. Will *et al.* [9] in their study had suggested that the osteoporosis in AS could well be a primary pathological event. Reduction in spinal mobility is unlikely to explain osteopenia of the femoral neck in these patients, as all the patients had normal hip joints. Previous studies have demonstrated that cortical bone is spared from the osteoporotic process in early disease [9, 10, 12]. This suggests that the osteoporosis is mainly due to involvement of the trabecular bone which is metabolically more active and thus more susceptible to cytokine and hormone influences than cortical bone. The role of cytokines in AS has been investigated, but no correlations were established [20]. The role of testosterone in AS is controversial with low, normal and high values reported [21–24]. In a separate study, we found no relationship between serum testosterone and osteoporosis associated with AS [25].

The clinical significance of osteoporosis lies in the development of fractures. An increased prevalence of vertebral fractures in patients with AS compared with age-matched controls has been described in another study [8]. The patients described in our study had a higher prevalence of vertebral fractures compared with a healthy control group, despite the fact that the controls were older. Our cohort of patients with AS was relatively young (mean age 37.2 yr). In comparison, the patient population described by Donnelly *et al.* [8] was older (mean age 43.5 yr). Since our age-matched control group would have been fairly young, we used the basic presumption that young healthy and normal males do not have spontaneous vertebral fractures and therefore elected not to subject them to the hazards of radiation. Instead, the control group selected were older males who had previously been characterized for another study [17] and already had vertebral radiographs available for evaluation. We demonstrated a higher prevalence of fractures in the AS patients compared with this group despite the fact that they had a higher possibility of fractures given their older age compared with the subjects with AS. This suggests that the disease process possibly contributes to accelerating fracture susceptibility in patients with AS. Besides, our patients did not have a history of trauma, which suggests that non-traumatic mechanisms such as osteoporosis may play an aetiological role.

We did not find a relationship between BMD of either the lumbar spine or femoral neck and the fractures. This result is consistent with previous findings of Donnelly *et al.* [8]. However, in their cohort of patients almost half had advanced radiographic changes in the spine and the presence of syndesmophytes may have

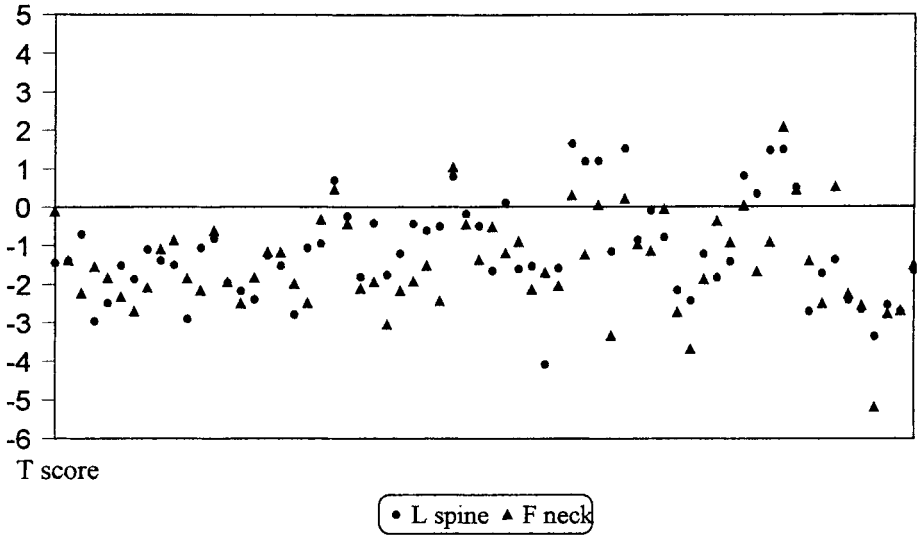

FIG. 1. *T* scores of the lumbar spine and femoral neck in patients with AS ($n = 66$). The World Health Organization defines osteopenia using BMD as a *T* score between -1.0 and -2.5 S.D., and osteoporosis as a *T* score below -2.5 S.D. below peak bone mass.

obscured the association. Pathological changes in AS occur predominantly in the spine and since structural alteration of the vertebral bodies may exist, it is possible that an association between BMD and fractures may not be apparent. However, the cohort of patients in this study did not have advanced spinal changes and therefore the lack of correlation between BMD and vertebral fractures is unlikely to be due to syndesmophytes. In this context, it is of note that a lack of relationship between BMD and vertebral fractures has also been observed in patients with rheumatoid arthritis [26], a condition in which the spine is virtually normal structurally although vertebral osteoporosis is well documented. The lack of an association between BMD of the lumbar spine and vertebral fractures in AS may partly be due to the fact that the measurement of anteroposterior BMD in the lumbar spine includes ligaments which may be calcified as well as cortical and trabecular bone, while the osteoporosis in early AS involves mainly trabecular bone. Lateral spine densitometry may have a greater diagnostic sensitivity as selective measurement of trabecular bone mass is possible [27]; osteopenia of vertebral bodies by quantitative computerized tomography despite the presence of extensive syndesmophytes has been described [10]. Second, this lack of association could also be attributed to the fact that the bone density of our patients with AS showed a wide range, thereby contributing to the lack of a statistically significant relationship between BMD and vertebral fractures. Finally, the prevalence of vertebral fractures using morphometric techniques can change depending on the criteria used, and this may well contribute to the lack of association seen between BMD and vertebral fractures. Compared with subjective qualitative assessment of radiographs, morphometry is a more reproducible method for the assessment of vertebral fractures. Unfortunately, there are limitations to the morphometric approach in defining vertebral fractures, as not all deformities identified morphometrically are due to vertebral fractures. Other spinal disorders may give rise to a change in vertebral shape, including congenital abnormalities and acquired deformities such as osteoarthrosis or Scheurmann's disease; however, these are uncommon. In addition, there is as yet no gold standard for vertebral fracture definition. This has led to the establishment of numerous criteria for characterizing fractures by different researchers, thereby leading to a varied prevalence of fractures depending on the criteria used. The lack of correlation of femoral neck BMD with vertebral fractures may be due to the fact that BMD measurements are site specific. For example, BMD of the lumbar spine or distal radius does not predict the risk of hip fractures as well as the BMD of the femoral neck [28].

The results of this study suggest that the risk of developing vertebral fractures increases with duration of disease in patients with AS despite absent or incipient syndesmophytes. The fact that these patients had osteopenia in the absence of advanced spinal changes suggests that the disease process may have a role in the development of osteoporosis before immobility has occurred. However, we did not find an association between vertebral fractures and BMD of the lumbar spine or femoral neck in these patients.

Acknowledgements

The authors wish to thank Dr Ashok Bhalla and Dr Francis Ring, Royal National Hospital for Rheumatic Diseases, Bath, UK, for their constructive criticism and suggestions and Dr Terence O'Neill, ARC Epidemiology Unit, Manchester, UK, for his suggestions and assistance with statistics.

References

1. Wilkinson M, Bywaters EGL. Clinical features and course of ankylosing spondylitis. Ann Rheum Dis 1958; 17:209–28.
2. Hunter T, Dubo H. Spinal fractures complicating ankylosing spondylitis. Ann Intern Med 1978;88:546–9.
3. Hunter T, Dubo HIC. Spinal fractures complicating ankylosing spondylitis: a long term study. Arthritis Rheum 1983;26:751–9.
4. Hanson CA, Shagrin JW, Duncan H. Vertebral osteoporosis in ankylosing spondylitis. Clin Orthop Rel Res 1971; 74:59–64.
5. Dilsen N. Romatizmal hastaliklarda vertebral osteoporoz hakkinda [Vertebral osteoporosis in rheumatic diseases]. Turk Tip Cemiyeti Mecumuasi 1964;30:362–70.
6. Ralston SH, Urquhart GDK, Brzeski M, Sturrock RD. Prevalence of vertebral compression fractures due to osteoporosis in ankylosing spondylitis. Br Med J 1990; 300:563–5.
7. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ III. Fracture risk in patients with ankylosing spondylitis: A population based study. J Rheumatol 1994;21:1877–84.
8. Donnelly S, Doyle DV, Denton A, Rolfe I, McCloskey EV, Spector TD. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. Ann Rheum Dis 1994;53:117–21.
9. Will R, Palmer R, Bhalla AK, Calin A. Osteoporosis in early ankylosing spondylitis: a primary pathological event? Lancet 1989;2:1483–5.
10. Devogelaer JP, Maldague B, Malghem J, de Deuxchaisnes CN. Appendicular and vertebral bone mass in ankylosing spondylitis. Arthritis Rheum 1992;35:1062–7.
11. Mitra D, Ring EFJ, Bhalla AK, Collins AJ. Osteoporosis associated with ankylosing spondylitis. In: Ring EFJ, ed. Current research in osteoporosis and bone mineral measurement III. London: British Institute of Radiology, 1994:42–3.
12. Mullaji AB, Upadhyay SS, Ho EKW. Bone mineral density in ankylosing spondylitis. J Bone Joint Surg 1994;76B:660–5.
13. Cummings SR, Black DM, Nevitt MC *et al.* Bone density at various sites for prediction of hip fractures. Lancet 1993;341:72–5.
14. Wasnich RD, Ross PD, Heilbrun LK, Vogel JM. Prediction of postmenopausal fracture risk with use of bone mineral density measurements. Am J Obstet Gynecol 1985;153:745.
15. Khan MA, van der Linden SM. AS and other spondyloarthropathies. Rheum Dis Clin North Am 1990;16:551.
16. Taylor HG, Wardle T, Beswick EJ, Dawes PT. The relationship of clinical and laboratory measurements to radiological change in ankylosing spondylitis. Br J Rheumatol 1991;30:330–5.
17. O'Neill TW, Felsenberg D, Varlow J *et al.* The prevalence of vertebral deformity in European men and women: The European Vertebral Osteoporosis Study. J Bone Miner Res 1996;11:1010–8.
18. Black DM, Cummings SR, Stone K, Hudes E, Palermo L, Steiger P. A new approach to defining normal vertebral dimensions. J Bone Miner Res 1991;6:883–92.
19. McCloskey EV, Spector TD, Eyres KS *et al.* The assessment of vertebral deformity: a method for use in population studies and clinical trials. Osteoporosis Int 1993; 3:138–47.
20. Bilgic A, Tutuncu ZN, Kennedy LG, Calin A. Interleukin-6, acute phase reactants and clinical status in ankylosing spondylitis. Ann Rheum Dis 1994;53:425–6.
21. Borbas E, Feher K, Hejj G, Gaal M, Balint G. Steroid hormone levels in peripheral sera of patients with ankylosing spondylitis. EULAR symposium 'Seronegative Polyarthritis', Rome. 1986(Abstract):120.
22. Dougados M, Nahoul K, Brasseur B, Amor B. Sex hormone levels in ankylosing spondylitis. EULAR symposium 'Seronegative Polyarthritis', Rome. 1986 (Abstract):121.
23. Spector TD, Ollier W, Perry LA, Silman AJ, Thompson PW, Edwards A. Free and serum testosterone levels in 276 males: A comparative study of rheumatoid arthritis, ankylosing spondylitis and healthy controls. Clin Rheumatol 1988;8:37–41.
24. Tapia-Serrano R, Jimenez-Balderas FL, Murrieta S, Bravo-Gatica C, Guerra R, Mintz G. Testicular function in active ankylosing spondylitis: therapeutic response to human chorionic gonadotrophin. J Rheumatol 1991; 18:841–8.
25. Mitra D, Elvins DM, Collins AJ. Testosterone and testerone free index in mild ankylosing spondylitis: relationship with bone mineral density and vertebral fractures. J Rheumatol 1999;26:2414–7.
26. Spector TD, Hall GM, McCloskey EV, Kanis JA. Risk of vertebral fracture in women with rheumatoid arthritis. Br Med J 1993;306:558.
27. Bronson W, Walker S, Allen S. Osteoporosis in ankylosing spondylitis (AS): 'hidden' loss of vertebral body bone mass detected by dual energy X-ray absorptiometry (DEXA). Arthritis Rheum 1992;35:S243.
28. Cummings SR, Black DM, Nevitt MC *et al.* Bone density at various sites for prediction of hip fractures. Lancet 1993;341:72–5.