Bone Mineral Density, Calcaneal Ultrasound, and Bone Turnover Markers in Women with Ankylosing Spondylitis

DEBORAH J. SPEDEN, ANDRE I. CALIN, FRANCIS J. RING, and ASHOK K. BHALLA

ABSTRACT. ***Objective.*** To assess bone mineral density (BMD) by dual energy x-ray absorptiometry (DEXA) and calcaneal quantitative ultrasound (QUS) in a cohort of pre- and postmenopausal women with ankylosing spondylitis (AS), and to determine any relationships with markers of bone turnover and disease activity or severity.

Methods. Fifty premenopausal and 16 postmenopausal women with AS were studied. Clinical and radiological status was assessed by the Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Bath AS Metrology Index (BASMI), and Bath AS Radiology Index (BASRI). BMD of the hip and spine was measured by DEXA, and QUS measured at the heel. Serum osteocalcin (OC), bone-specific alkaline phosphatase (BALP), urinary D-pyridinoline crosslinks (D-PYR), and C-reactive protein (CRP) were assayed.

Results. Women with AS (n = 66) had reduced BMD at the hip compared to age and sex matched controls (n = 132). The mean t scores were –1.1 and –2.0, and z scores –0.4 and –0.37, for pre- and postmenopausal women, respectively. Four (6%) had osteoporosis and 34 (52%) had osteopenia according to the WHO definitions. Using a multiple regression model, femoral neck BMD was found to be significantly affected by age, body mass index, and the sacroiliac radiographic score. There were no significant correlations of BMD with disease duration or disease activity. QUS measures did not correlate with DEXA measures of BMD. Women with AS had significantly lower markers of bone formation, OC and BALP, and a trend to higher D-PYR than controls. Serum OC levels correlated negatively with femoral neck BMD, whereas D-PYR correlated with CRP levels.

Conclusion. Women with AS have reduced hip BMD, 0.39 SD below age and sex matched controls. Bone turnover in women with AS is characterized by low OC and BALP. (J Rheumatol 2002; 29:516–21)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS OSTEOPOROSIS BONE MINERAL DENSITY
QUANTITATIVE ULTRASOUND BONE TURNOVER MARKERS

A decrease in bone density of the axial skeleton is a feature of ankylosing spondylitis (AS), with an increase in prevalence of vertebral fracture[1,2]. Low bone mineral density (BMD) of the lumbar spine (LS) and hip has been noted in mild disease with minimal radiological changes, with a mean reduction in BMD of 10% compared with controls[3,4]. BMD at the hip may be a more reliable indicator of axial BMD in established AS due to elevation of anteroposterior lumbar spine BMD by paraspinal ossification and syndesmophyte formation in more advanced disease[5,6].

Dual energy x-ray absorptiometry (DEXA) has generally been used to measure BMD of the spine, hip, and radius in AS. Recently, quantitative ultrasound (QUS) has generated interest in the assessment of bone density, but has not been used to evaluate patients with AS. This method has advantages in terms of cost, portability of equipment, and lack of ionizing radiation. Calcaneal ultrasound measures mainly trabecular bone indices, but this distal site may not reflect changes in axial trabecular bone. Calcaneal ultrasound has been shown to predict the risk of osteoporotic hip and nonvertebral fractures in elderly populations[7,8].

The pathogenesis and timing of onset of osteoporosis in AS remain unclear. Both increased and decreased bone turnover have been reported, utilizing various markers of bone turnover[9-12]. Bone-specific serum alkaline phosphatase (BALP) and osteocalcin (OC) are sensitive and specific markers of bone formation. D-pyridinoline (DPYR) crosslinks of collagen molecules excreted in urine are a useful measure of bone resorption. Bone formation and resorption are normally tightly coupled.

Studies of BMD in AS have included few women, despite the prevalence of AS having a female:male ratio of

From the Royal National Hospital for Rheumatic Diseases, Bath, UK.

Supported by the National Osteoporosis Society, UK.

D.J. Speden, MBBS, FRACP, Clinical Research Fellow; A. Calin, MD, FRCP, Consultant Rheumatologist; F.J. Ring, DSc, Head, Clinical Measurement Department, A.K. Bhalla, MD, FRCP, Consultant Rheumatologist.

Address reprints requests to Dr. D.J. Speden, Wrightington Hospital, Hull Lane, Appley Bridge, near Wigan, Lancashire WN6 9EP, UK. E-mail: debspeden@hotmail.com

Submitted March 5, 2001; revision accepted September 7, 2001.

1:3. Osteoporosis, however, has a higher prevalence in women, with increasing risk after menopause and with age. We assessed BMD by DEXA and quantitative calcaneal ultrasound in a cohort of pre- and postmenopausal women, and investigated relationships with markers of bone turnover and disease activity or severity.

MATERIALS AND METHODS

A cross sectional study was conducted between October 1997 and March 1999. Sixty-six women aged between 20 and 75 years consented to take part, as approved by the local ethics committee. All subjects had a diagnosis of primary AS, according to the modified New York criteria[13]. Women were categorized as premenopausal, defined by a regular menstrual cycle, or postmenopausal (12 months amenorrhea after menopause). Women who had a hysterectomy and were aged less than 55 years, or whose menopausal status was otherwise unclear, were excluded from study. Subjects with any condition such as thyroid disease or malabsorption, or taking any medication such as hormone replacement therapy (HRT), oral corticosteroids (in continuous oral doses for > 3 mo), or anticonvulsants that might affect bone turnover were excluded. Subjects who had had intermittent intraarticular steroid injections or steroid eye drops for uveitis were not excluded. Other exclusions were pregnancy, bilateral total hip replacements, or psoriatic and inflammatory bowel related spondyloarthropathy. Data from 132 age and sex matched healthy controls (with no condition or medication, including HRT, known to affect bone metabolism) were obtained from a database of measurements of BMD and bone turnover of the normal population in the local Bath region.

Demographic data, height and weight, and disease duration were recorded. Current dietary calcium intake was recorded in terms of daily intake of dairy products, where 1 cup of milk or 60 g (2 ounces) of cheese was equated to 300 mg calcium. The subjects' disease activity, functional index, and physical measures were assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[14], Bath Ankylosing Spondylitis Functional Index (BASFI)[15], and the Bath Ankylosing Spondylitis Metrology Index (BASMI)[16], respectively. Anteroposterior (AP) and lateral lumbar spine and sacroiliac radiographs taken within the last 2 years were examined and scored according to the Bath Ankylosing Spondylitis Radiology Index (BASRI) criteria[17] by a single unblinded investigator (DS). BMD (g/cm^2) at the AP lumbar spine (L1–L4), nondominant hip, and whole body was measured using a Hologic QR4500 (Version 8) densitometer. *In vivo* precision was 1.0% at AP lumbar spine, 1.8% at femoral neck, 0.82% for whole body scans. T and z scores (standard deviations from peak adult BMD and age matched BMD, respectively) were related to the Hologic database, based on US women[18].

Calcaneal ultrasound using a Sahara Clinical Bone Sonometer (Hologic) was undertaken in 23 women after the sonometer was obtained by the Clinical Measurement Department of our hospital in late 1998. The patient's left heel was placed between 2 transducers covered with silicon rubber pads and direct contact ensured by the use of a coupling gel. QUS measures the speed at which sound propagates through bone (SOS), and the pattern of attenuation of ultrasonic frequencies in bone (BUA). Stiffness (QUI) is calculated from a combination of BUA and SOS using the equation: stiffness = $(0.67 \times \text{BUA} + 0.28 \times \text{SOS}) - 420$. Accuracy and precision may be affected by positioning and other variables of the measurement region. In this institution, the coefficient of variation for BUA is 3.5% and for SOS it is 1.2%.

Blood and urine samples were collected from 40 women with AS and 74 age matched healthy control women who were able to attend prior to 10 AM. Samples were assayed for C-reactive protein (CRP) by latex enhanced turbimetry using Roche Integra equipment in the hospital's clinical chemistry department, or stored at –70°C for measurement of bone turnover markers. BALP, OC, and urinary freeD-PYR crosslinks were assayed in duplicate by ELISA, using Alkphase-B, Novocalcin, and Pyrilinks-D kits, respectively, from Metra Biosystems, Mountain View, CA, USA. D-PYR crosslinks are reported as nmol/mmol creatinine. Intraassay coefficient of variation were < 10% in all assays.

Statistical analyses were performed in several steps: (1) The study population was described in terms of demographic, clinical, and radiological data, and results expressed as mean (standard deviation) or percentages. Student t test was used to assess differences in this data between pre- and postmenopausal women. (2) BMD and bone turnover markers of the AS and control groups were compared using Student t test for paired samples. (3) The proportion of women in the AS and control groups who met the WHO criteria for osteoporosis and osteopenia were compared by chi-squared test. (4) Univariate analysis was conducted in which the dependent variable was the femoral neck and lumbar spine BMD and the independent variables were age, BMI, and disease severity and disease activity indices. A multiple regression model was then fitted using backward selection to determine factors affecting BMD. Similar modeling was used to assess osteoporotic risk factors and BMD. Univariate analyses were used to evaluate correlations between BMD and QUS, bone turnover markers, and CRP. SPSS Version 8.0 was used for these analyses. (6) The level of statistical significance was < 0.05.

RESULTS

The subjects' demographic data are summarized in Table 1. Eighty percent (53/66) of women with AS were taking nonsteroidal antiinflammatory drugs. Two premenopausal women were taking sulfasalazine for peripheral joint symptoms, but no other disease modifying drugs were being taken. In the postmenopausal group, 10 women were between 1 and 5 years postmenopause, 2 were 5–10 years postmenopause, 4 were > 10 years postmenopause. As expected, postmenopausal women had longer disease duration and more severe radiological disease. BASMI, but not BASFI or BASDAI, correlated with radiological severity (sacroiliac score, $r = 0.61$, $p < 0.0001$; lumbar spine score, $r = 0.71$, $p < 0.0001$). Body mass index (BMI) and CRP levels were not significantly different between pre- and postmenopausal women. The healthy control women were age matched to the women with AS [mean age 43.07 (SD 10.8) vs 43.4 (10.6) yrs in the AS group; $p = 0.85$, NS]. The BMI of the control group was not significantly different from that of the AS group [mean BMI 24.2 (SD 3.6) vs 25.5 (5.3); $p = 0.17$, NS].

Bone mineral density. BMD of 132 healthy age matched local women, used as the control group, were compared to the Hologic database. There was no significant difference between the 2 groups at the lumbar spine and hip sites. T and z scores for the lumbar spine and hip regions were therefore derived from the Hologic database. Both pre- and postmenopausal women with AS had significantly lower BMD at the femoral neck and total hip than controls (Table 2). From Table 2 it can be seen that pre- and postmenopausal women with AS have mean t scores of –1.1 and –2.0, respectively; however, the z score remains relatively constant at –0.39, indicating that there is not a progressive deviation of BMD from control levels with increasing age in women with AS.

There was no significant difference in AP lumber spine BMD of women with AS compared to the local controls.

Table 1. Clinical and radiological characteristics of women with AS. Data presented as mean (SD) or numbers of patients (percentage).

Variable	All	Premenopausal	Postmenopausal	p*
N	66	50	16	
Age, yrs	43.4 (10.6)	38.9 (7.4)	57.1 (6.7)	0.0001
Disease duration, yrs	21.1 (5.3)	17 (8.2)	33.9 (12.2)	0.0001
BMI, kg/m^2	25.5 (5.3)	25.3 (5.8)	26.3 (3.6)	0.66 NS
BASMI, 0–10	2.7 (1.9)	2.1 (1.6)	4.4 (1.8)	0.0001
BASDAI, 0–10	4.0 (2.2)	3.9 (2.3)	4.4 (1.8)	0.38 NS
BASFI, 0–10	3.3 (2.5)	3.0 (2.6)	4.2 (1.9)	0.08 NS
Sacroiliitis only, normal spine radiograph (%)	28/66 (42)	27/50 (54)	1/16 (6)	
SI score, 0–4	3.0 (0.8)	3.0 (0.8)	4.0 (0.5)	0.0004
LS score, 0–4	2.0 (1.5)	1.5 (1.0)	3.0 (0.9)	0.0001
CRP, mg/l	8.6 (5.0)	9.7 (11.9)	7.6 (13.9)	0.65 NS
Abnormal CRP (%)	20/45 (44)	17/36 (47)	3/9 (33)	

* Comparing pre- and postmenopausal, t test. SI: Sacroiliac, LS: lumbar spine, NS: not significant

The controls, however, had significantly higher whole body BMD measures than the Hologic database [mean 1.13 (SD 1.0) vs 1.05 (0.09); $p < 0.05$, t test]. Women with AS had significantly lower whole body BMD compared with local controls, but not when compared to the Hologic database (Table 2). Due to the disparity between the 2 control groups, no further analyses were performed on the whole body BMD data.

According to the WHO definition of osteoporosis[19], 4 (6%) women with AS had osteoporosis at the femoral neck and a further 34 (52%) met the criteria for osteopenia. At the lumbar spine, 5 (8%) were osteoporotic and 12 (18%) were osteopenic. Significantly more women with AS were osteopenic at the hip or osteoporotic at the hip and lumbar spine than the control group (Table 3). Four women had had prior nontraumatic fractures (one hip at age 45, one ankle at age 46, 2 wrist fractures at ages 63 and 64). The subjects who had sustained wrist fractures both had osteoporosis at the lumbar spine, and one also met the criteria for osteoporosis at the femoral neck. The 2 other subjects were osteopenic at the femoral neck, but not at the lumbar spine. In terms of other independent risk factors for osteoporosis, 7 subjects (2 postmenopausal) had a family history of osteoporosis; 13 (2 postmenopausal) had a body weight < 57.7 kg (127 lb); 13 subjects (2 postmenopausal) were current smokers. Fifty percent (25/50) of premenopausal women and 40% (6/16) of postmenopausal women had dietary intakes of calcium that were less than the recommended

Table 2A. BMD of premenopausal women with AS and controls.

	AS, n = 50, mean (SD)	Control, n = 100 mean (SD)	p*	% Difference	T Score	Z Score
Age	39.0 (7.4)	38.6 (7.4)	NS			
Lumbar spine	1.05 (0.16)	1.05 (0.12)	NS		–0.11	0.35
Femoral neck	0.81 (0.11)	0.86 (0.11)	0.01	5.8%↓	–1.10	–0.40
Total hip	0.91 (0.12)	0.96 (0.12)	0.02	5.0%↓	–0.64	–0.29
Whole body	1.11 (0.07)	1.15 (0.09)	0.02	3.1%↓	0.03	0.55

* Student t test, NS: not significant.

Table 2B. BMD of postmenopausal women with AS and controls.

	AS, n = 16, mean (SD)	Control, n = 32, mean (SD)	p*	% Difference	T Score	Z Score
Age	57.0 (6.7)	57.1 (6.0)	NS			
Lumbar spine	0.95 (0.19)	0.95 (0.14)	NS		–0.79	0.57
Femoral neck	0.69 (0.07)	0.76 (0.13)	0.02	9.4%↓	–2.03	–0.37
Total hip	0.80 (0.08)	0.89 (0.12)	0.02	9.6%↓	–1.39	–0.24
Whole body	1.03 (0.07)	1.09 (0.10)	0.08	5.4%↓	–0.81	0.13

* Student t test, NS: not significant

Table 3. Osteopenia and osteoporosis in lumbar spine, femoral neck, and total hip regions in women with AS and controls matched for age and sex.

Femoral Neck T Score	AS, n = 66 (%)	Controls, n = 132 (%)
Normal (T score > –1.0 SD)	28 (42)	80 (61)
Osteopenia (–2.5 < T score < –1.0)	34 (52)	48 (36)
Osteoporosis (T score < –2.5)	4 (6)	4 (3)
Chi-squared test: p = 0.05		
Total Hip T Score	**AS, n = 66 (%)**	**Controls, n = 132 (%)**
Normal (T score > –1.0 SD)	40 (61)	100 (76)
Osteopenia (–2.5 < T score < –1.0)	23 (35)	31 (23)
Osteoporosis (T score < –2.5)	3 (4)	1 (1)
Chi-squared test: p = 0.04		
Lumbar Spine T Score	**AS, n = 66 (%)**	**Controls, n = 132 (%)**
Normal (T score > –1.0 SD)	49 (74)	100 (76)
Osteopenia (–2.5 < T score < –1.0)	12 (18)	31 (23)
Osteoporosis (T score < –2.5)	5 (8)	1 (1)
Chi-squared test: p = 0.03		

daily allowance of 1500 mg/day. Body weight ($p < 0.0001$ for femoral neck and $p = 0.02$ for lumbar spine) and history of fracture ($p = 0.005$ for femoral neck; $p = 0.002$ for lumbar spine) were found to be factors predicting femoral neck and lumbar spine BMD using a multiple regression model.

Using a multiple regression model fitted using backward selection, the following variables were found to significantly affect femoral neck BMD: age ($r = –0.35$, $p = 0.003$), BMI ($r = 0.35$, $p = 0.001$), and sacroiliac radiographic score ($r = –0.29$, $p = 0.013$). Measures of disease activity (BASDAI, BASFI, CRP) had no significant correlations with femoral neck BMD. Similar effects of age ($r = –0.39$, $p = 0.005$) and BMI ($r = 0.39$, $p = 0.002$) were found on lumbar spine BMD. Lumbar spine BMD also correlated with BASMI ($r = 0.44$, $p = 0.004$).

Calcaneal ultrasound. Twenty-three women (18 premenopausal, 5 postmenopausal) with AS had calcaneal quantitative ultrasound. There was a trend for QUI and SOS to correlate with femoral neck and total hip BMD, but this was only significant for calcaneal SOS and hip BMD ($r = 0.43$, $p = 0.04$).

Bone turnover markers. The results of bone turnover markers in 40 women with AS and 74 controls are shown in Table 4. Women with AS had significantly lower BALP [mean 15.0 (SD 4.8) vs 17.3 (6.2); $p = 0.03$, t test] and OC [mean 7.5 (SD 2.9) vs 9.6 (4.3); $p = 0.02$, t test] than controls, with a nonsignificant trend to raised D-PYR [mean 9.4 (SD 5.2) vs 7.7 (3.8); $p = 0.08$, t test]. Postmenopausal women in both the AS and control groups had higher BALP than premenopausal women [mean 19.2 (SD 3.6) vs 14.3 (4.6); $p > 0.005$, t test, data not shown]. Serum OC correlated negatively with femoral neck BMD ($r = –0.29$, $p = 0.004$) and total hip BMD ($r = –0.44$, $p = 0.01$). No correlation was observed between any marker of bone turnover and calcaneal US measures.

Table 4. Bone turnover markers of women with AS and controls.

	AS	Control	p*
Number	40	74	
Age, yrs	41.6 (10.1)	44.6 (12.1)	NS
BALP, U/I	15.0 (4.8)	17.3 (6.2)	0.03
OC, ng/ml	7.5 (2.9)	9.6 (4.3)	0.02
DPYR/creatinine, nmol/l	9.4 (5.2)	7.7 (3.8)	0.08

* Student t test, NS: not significant

C-reactive protein. Forty-four percent (20/45) of women with AS had a CRP greater than the normal range (< 5.0 mg/dl) measured on a single occasion. Those with a raised CRP had significantly higher BASDAI [mean 5.0 (SD 2.0) vs 3.2 (2.0); $p = 0.004$, t test] and BASFI [mean 4.3 (SD 2.5) vs 2.3 (2.0); $p = 0.005$, t test] compared with those women with AS who had CRP levels within normal limits. D-PYR, but not OC or BALP, correlated with CRP levels ($r = 0.45$, $p = 0.01$). There were no relationships between CRP and BMD or QUS.

DISCUSSION

This study reports BMD, QUS, and bone turnover marker data in a large cohort of women with AS. Such data have not previously been reported in a specifically female study, including both pre- and postmenopausal women. Our findings confirm that women with AS have a reduced hip BMD of 0.39 SD below age and sex matched controls, consistent with Donnelly's report, which included 25 women[2]. Overall, 58% of subjects were osteopenic or osteoporotic at the femoral neck, with a similar figure reported in a mixed sex study[11]. We did not find a progressive decrease in hip BMD with disease duration independent of age related loss, although the radiological severity of sacroiliac disease was an independent factor in predicting femoral neck BMD. Our findings could be explained by early bone density loss associated with AS, or the achievement of a lower peak bone mass, with the normal pattern of age related loss occurring thereafter. The cross sectional design is a limiting factor in this study, and serial measurements of bone density and markers of bone turnover, particularly early in the disease course, would be necessary to address this issue.

Low hip BMD is a feature of AS in both men and women. In this study, BMD at the femoral neck in premenopausal

women was around 5% lower than controls. Femoral neck BMD in men with AS has been reported as around 10% lower than controls[3,5,6], with z scores of around –1.0[2,4]. The less marked reduction of BMD in women could be explained by either a lower inflammatory disease activity in women or more efficient hormonal bone protection. BMD at the lumbar spine was not significantly different from control groups in this study. It has been shown that anteroposterior lumbar spine BMD does not represent trabecular BMD in AS patients with advanced disease, both men and women, due to false elevation by paraspinal ossification and syndesmophyte formation[20]. The correlation between lumbar spine BMD and BASMI presumably reflects the changes in DEXA and spinal mobility induced by syndesmophyte formation. Quantitative computer tomography[21] and lateral lumbar spine DEXA[6] have shown low trabecular bone density in the presence of elevated anteroposterior lumbar spine DEXA, but use of these techniques is limited by radiation dose and technical difficulties, respectively. Overall, the presence of axial demineralization is more readily assessed by hip BMD[6]. However, hip involvement in AS and its effect on hip BMD has not been examined in this or other studies — whether hip involvement may have an effect on hip BMD measurements is unclear.

Quantitative ultrasound assesses alternative variables to DEXA at peripheral skeletal sites. The lack of consistent correlations between BMD and QUS we observed could be due to the smaller number of calcaneal ultrasounds that we were able to perform. BMD of the calcaneus may be a better measure to assess the relationship between QUS and BMD measurements, as the calcaneum may not reflect axial disease processes in AS. Calcaneal BUA has been reported to show moderate correlation with hip and lumbar spine BMD in a non-AS population[22,23]. Calcaneal ultrasound has been shown to discriminate between patients with and without osteoporotic hip fracture[7], but a definition of osteoporosis using ultrasonic variables is still lacking.

The pathogenesis and timing of onset of osteoporosis in AS remains unclear. A reduced range of movement of the spine in ankylosing patients has been proposed as an etiological factor in AS, but low spine and hip BMD has been reported in mild disease with minimal radiological changes[3,4]. Low bone density as an early feature of AS suggests that inflammatory or systemic mediators may be involved. Inflammatory markers have been found to correlate with markers of bone metabolism[10,12,24,25]. CRP correlated with D-PYR, a marker of bone resorption, in this study, and there was also correlation between CRP and clinical indices of disease activity, BASDAI, and BASFI. The lack of consistent correlation between CRP, bone turnover markers, and BMD may be due to these variables reflecting different time courses: CRP and bone turnover markers measure the current status of inflammation and bone metabolism, whereas BMD is a longitudinal variable.

The low osteocalcin, together with the trend to elevation of D-PYR, in our study suggests there is uncoupling of bone turnover. The negative correlation of serum OC with BMD at the hip, in the presence of overall lower OC levels, suggests inappropriately low bone formation. If AS is associated with an inherently low bone turnover, we could hypothesize that increased bone resorption driven by inflammatory mediators would result in uncoupled bone turnover. A reduced bone turnover has previously been suggested on the basis of normal urinary calcium/creatinine ratios[3] and decreased osteocalcin[9,10], although osteocalcin levels were normal in other studies[6,11,12,25]. Histomorphometric analysis of iliac crest biopsies has also suggested that reduction in bone formation may be a factor in osteoporosis in AS[26]. Other studies[11,27] have suggested increased bone turnover as the primary factor. Although elevated levels of pyridinoline crosslinks have been reported[11,12,28], D-PYR has also been found in normal levels[6,10,24]. This variation in reports on markers of bone metabolism may reflect the heterogeneity of disease activity in the patient population at the time of study. Longitudinal studies of bone metabolism, together with assessments of disease activity such as serial CRP measures, in AS may provide more meaningful data.

From this large cohort of women with ankylosing spondylitis, we conclude that women with AS at any age have a significantly lower BMD at the hip than their age and sex matched controls when assessed by DEXA. There is no correlation between BMD at the hip and disease duration, suggesting that low BMD is an early feature of disease. While higher rates of vertebral fracture have been reported[1,2,29], the predictive value of BMD for fracture in AS remains undefined.

ACKNOWLEDGMENT

The authors wish to acknowledge D. Elvins, J. Hueting, J. Stott, and M. Minchinton of the Clinical Measurements Department, RNHRD, for their technical support; and G. Taylor, statistician, for providing statistical advice.

REFERENCES

1. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 1994;21:1877-82.
2. 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.
3. Will R, Palmer R, Bhalla AK, Ring F, Calin A. Osteoporosis in early ankylosing spondylitis: a primary pathological event? Lancet 1989;2:1483-5.
4. Mitra D, Ring FJ, Bhalla AK, Collins A. Osteoporosis associated with ankylosing spondylitis. In: Ring EFJ, Elvins AK, Bhalla AK, editors. Current Research in Osteoporosis and Bone Mineral Density III, 1994.
5. Mullaji AB, Upadhyay SS, Ho EK. Bone mineral density in ankylosing spondylitis. DEXA comparison of control subjects with mild and advanced cases. J Bone Joint Surg Br 1994;76:660-5.

6. Bronson WD, Walker SE, Hillman LS, Keisler D, Hoyt T, Allen SH. Bone mineral density and biochemical markers of bone metabolism in ankylosing spondylitis. J Rheumatol 1998;25:929-35.
7. Hans D, Dargent-Molina P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. Lancet 1996;348:511-4.
8. Pluijm S, Graafmans W, Bouter L, Lips P. Ultrasound measurements for the prediction of osteoporotic fractures in elderly people. Osteoporosis Int 1999;9:550-6.
9. Franck H, Keck E. Serum osteocalcin and vitamin D metabolites in patients with ankylosing spondylitis. Ann Rheum Dis 1993;52:343-6.
10. Mitra D, Elvins DM, Collins AJ. Biochemical markers of bone metabolism in mild ankylosing spondylitis and their relationship with bone mineral density and vertebral fractures. J Rheumatol 1999;26:2201-4.
11. El Maghraoui A, Borderie D, Cherruau B, Edouard R, Dougados M, Roux C. Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. J Rheumatol 1999;26:2205-9.
12. Marhoffer W, Stracke H, Masoud I, et al. Evidence of impaired cartilage/bone turnover in patients with active ankylosing spondylitis. Ann Rheum Dis 1995;54:556-9.
13. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
14. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
15. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
16. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis. The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
17. MacKay K, Mack C, Brophy S, Calin A. The Bath Ankylosing Spondylitis Radiology Index: a new, validated approach to disease assessment. Arthritis Rheum 1998;41:2263-70.
18. Kelly T. Bone mineral density reference databases for American men and women. J Bone Miner Res 1990;5:S249.
19. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137-41.
20. Donnelly S, Jawed S, Meija A, Doyle DV. Effect of syndesmophyte formation on lumbar spine bone density in patients with ankylosing spondylitis. Br J Rheumatol 1995;34 Suppl:117.
21. Devogelaer JP, Maldague B, Malghem J, Nagant de Deuxchaisnes C. Appendicular and vertebral bone mass in ankylosing spondylitis. A comparison of plain radiographs with single- and dual-photon absorptiometry and with quantitative computed tomography. Arthritis Rheum 1992;35:1062-7.
22. Tromp AM, Smit JH, Deeg JH, Lips P. Quantitative ultrasound measurements of the tibia and calcaneus in comparison with DXA measurements at various skeletal sites. Osteoporosis Int 1999;9:230-5.
23. 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.
24. MacDonald AG, Birkinshaw G, Durham B, Bucknall RC, Fraser WD. Biochemical markers of bone turnover in seronegative spondylarthropathy: relationship to disease activity. Br J Rheumatol 1997;36:50-3.
25. Toussirot E, Ricard-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. Szejnfeld VL, Monier-Faugere MC, Bognar BJ, Ferraz MB, Malluche HH. Systemic osteopenia and mineralization defect in patients with ankylosing spondylitis. J Rheumatol 1997;24:683-8.
27. Acebes C, de la Piedra C, Traba ML, et al. Biochemical markers of bone remodeling and bone sialoprotein in ankylosing spondylitis. Clin Chim Acta 1999;289:99-110.
28. Yilmaz N, Ozaslan J. Biochemical bone turnover markers in patients with ankylosing spondylitis. Clin Rheumatol 2000;19:92-8.
29. Mitra D, Elvins DM, Speden DJ, Collins AJ. The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. Rheumatology 2000;39:85-9.