Bone Loss Is Detected More Frequently in Patients with Ankylosing Spondylitis with Syndesmophytes

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ABSTRACT. ***Objective.*** To define the relationship between bone growth (syndesmophytes) and bone loss (osteoporosis) in ankylosing spondylitis (AS).

Methods. Bone mineral density (BMD) at the spine, hip, and radius was measured by dual-energy x-ray absorptiometry (DEXA), dual-energy quantitative computed tomography (DEQCT), and peripheral quantitative computed tomography (pQCT) in 103 patients with AS. Radiographs of the lumbar spine were used to detect syndesmophytes. Patients were divided in 3 groups according to disease duration.

Results. Osteopenia at the hip and spine was found by DEXA in 56% and 41%, respectively, of the patients with disease duration < 5 years (n = 27), with an additional 11% and 15% having osteoporosis. In patients with a longer disease duration, > 10 years (n = 28), 29% were osteoporotic at the hip and only 4% at the lumbar spine. In contrast, using spinal DEQCT, 59% of patients with early disease were found to be osteopenic; 36% of patients with long-standing disease were osteopenic and 18% were osteoporotic. More than half the patients (55%) had syndesmophytes (n = 55). With spinal DEQCT there were more patients with syndesmophytes (63%) in the group with reduced bone density than in the group without (45%). This was similar with DEXA measurements at the hip, where 31% compared to 14% had osteoporosis, respectively. Osteocalcin was elevated in 34% of patients, but was not associated with disease activity or BMD.

Conclusion. The majority of patients with AS had reduced bone density. The method of bone density measurement is critical and should be different depending on disease duration. The finding that more patients with syndesmophytes had reduced bone density than those without suggests that bone growth and bone loss occur in parallel, and the role of inflammation in this process warrants further investigation. (J Rheumatol 2005;32:1290–8)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS OSTEOPOROSIS SYNDESMOPHYTES

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease that frequently runs a chronic course[1], often with a poor prognosis[2]. While the inflammatory process initially involves mainly the sacroiliac joints, the vertebral column is typically affected in later stages of the disease[3]. Alongside spinal inflammation, new bone growth leads to the formation of syndesmophytes and ankylosis of vertebrae[4]. Magnetic resonance imaging (MRI) to detect spinal inflammation and conventional radiographs to detect bone growth are the methods of choice for imaging[5,6].

Low bone density in patients with AS has been reported by several groups[7,8]. Osteodensitometry has been performed by different methods, such as dual-energy x-ray absorptiometry (DEXA), dual-energy quantitative computed tomography (DEQCT), and peripheral quantitative computed tomography (pQCT), and at different locations including the spine, the hip, and the forearm[9-11]. The performance of these techniques is known to vary and study results have not been consistent, partly because patient numbers have been low, preventing subgroup analyses. However, it is known that spinal DEXA measurements may give false-positive results, possibly related to new bone formation[12,13].

Patients with AS have an increased risk for spinal fracture[14-16], and the typical hyperkyphosis of AS is partly caused by vertebral fractures[17], contributing to functional loss[18].

Exactly how and why there might be loss of bone mineral content and new bone formation occurring in parallel in AS is unclear. It has been suggested that the pathologic processes of resorption and bone formation may well occur in close proximity[19].

This study was performed in a large group of AS patients at different stages of disease, including relatively early patients, to study bone density and its association with the presence of radiological syndesmophytes, in relation to disease duration, age, sex, and disease activity as assessed by the Bath AS Disease Activity Index (BASDAI)[20], the Bath

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AS Functional Index (BASFI)[21], and C-reactive protein (CRP).

MATERIALS AND METHODS

Patients. Patients were recruited consecutively from the University Hospital outpatient clinic in Berlin, Germany. All patients were asked to fill out disease-specific questionnaires to assess disease activity (BASDAI[20]) and function (BASFI[21]). Disease duration was assessed from the time of first symptoms.

Imaging. New bone formation was assessed as the presence of definite syndesmophytes, as observed by radiography of the lumbar spine in 2 planes (anteroposterior and lateral). Bone density was measured by DEXA (Hologic QDR 2000 plus, Hologic, Waltham, MA, USA) at the lumbar spine L2–L4 and the femoral neck, and judged according to the World Health Organization (WHO) guidelines by T scoring[22], adjusted for sex and age. Osteopenia was defined as a T score < –1, and osteoporosis as a T score < –2.5. The lumbar spine was also measured (mg/cm^3) by DEQCT (Somatom Plus 4, Siemens, Germany). Osteopenia was defined as density between 80 and 120 mg/cm^3 and osteoporosis as density < 80 mg/cm^3, as defined by Kalender, *et al* on this machine[23]. Bone density (mg/cm^3) at the dominant ultra distal radius was measured by pQCT (Stratec XCT 900, Stratec GmbH, Pforzheim, Germany). All bone mineral density (BMD) measurements were made on the same densitometers in a single center, using normal values supplied by the manufacturer to estimate T scores for DEXA measures.

Laboratory measurements. Serum concentrations of C-reactive protein (CRP, mg/l), alkaline phosphatase (ALP, U/l), 25-OH-vitamin D, parathyroid hormone (ng/l), osteocalcin (µg/l), and urinary deoxypyridinoline:creatinine ratio (nmol/mmol) were measured in the central laboratory of the clinic by established methodology.

Statistical analysis. The statistical program SPSS for Windows, version 8.0, was used for all analyses. The chi-square test was used for comparison of proportions between groups. Spearman's nonparametric correlation coefficients were calculated to compare measurements. Multiple regression was carried out using a backwards method to correct for age and disease duration where appropriate.

RESULTS

Patient characteristics. There were 103 patients in the study, all fulfilling the 1984 New York criteria for diagnosis of AS[24]. There were 64% men (n = 66) and 36% women (n = 37). Over 90% of the patients were HLA-B27-positive (n = 95). Less than 10% of patients had a history of corticosteroid use.

Patients were divided into 3 groups; Group 1: patients with disease duration ≤ 5 years; Group 2: patients with disease duration 5–10 years; and Group 3: patients with a disease duration > 10 years.

Table 1 gives data on patients' sex, age, disease duration, and the relative percentages of HLA-B27 in the groups. As there was an equal proportion of men and women in all groups, calculations have been made without correcting for sex.

According to the defined difference in disease duration the mean age was lowest in Group 1 and highest in Group 3 as expected. Function was not different across the groups. Laboratory measures were not different between groups (Table 2).

Prevalence of osteopenia and osteoporosis. Figure 1 shows the percentages of patients found to be osteopenic or osteoporotic with each method of bone density measurement. Osteoporosis was found most frequently with DEXA of the femoral neck, in over half of the patients studied. Peripheral QCT at the radius was normal in 83%.

Relationship between bone density measured by different techniques. There was no statistically significant difference between DEQCT- and DEXA-defined osteopenia or osteoporosis at the lumbar spine in the total cohort of AS patients (chi-square = 2.35, p = 0.13). Low bone density (osteopenia or osteoporosis) was significantly more common at the femoral neck (measured by DEXA) than at the lumbar spine as measured by either DEXA (chi-square = 20.11, p < 0.001) or by DEQCT (chi-square = 9.76, p < 0.01), suggesting that DEXA at the femoral neck is more sensitive for measuring osteoporosis in AS patients than spinal BMD measures. In comparison to the data obtained at other sites, bone density measurements at the forearm clearly classified fewer AS patients as osteopenic or osteoporotic (DEXA lumbar spine chi-square = 17.93, p < 0.0001; DEXA femoral neck chi-square = 72.59, p < 0.0001; and DEQCT lumbar spine chi-square = 30.64, p < 0.0001).

Correlation between T scores (by DEXA) at the lumbar spine and the neck of femur was good (Spearman correlation coefficient r = 0.69, p = 0.003). The results of DEQCT measurements (mg/cm^3) at the lumbar spine correlated less well, but still significantly with the T scores (by DEXA) at the femoral neck (r = 0.39, p = 0.03). Correlation between DEXA T scores at the lumbar spine and DEQCT at the lumbar spine was not significant (r = 0.13, p = 0.3). There was no correlation between bone density measured at the forearm (g/cm^3) and DEXA values at either lumbar spine (p = 0.18) or femoral neck (p = 0.8) or DEQCT values at the lumbar spine (p > 0.05).

There was no correlation between bone density measurements using different techniques and disease duration (all p > 0.4, data not shown), age (all p > 0.12, data not shown), BASDAI, BASFI, or CRP. Multiple regression using disease duration as a continuous variable (corrected for age and sex) did not change the results, with no significant relationship seen between disease duration and DEQCT (T = –0.966, p = 0.34), DEXA of lumbar spine (T = 0.458, p = 0.65), or DEXA of femoral neck (T = –1.954, p = 0.054).

Relationship between bone density and disease duration. Raw values and T scores for each assessment method are given in Table 3, and proportions of patients classified as osteopenic or osteoporotic are given in Table 4. At the lumbar spine, all groups were osteopenic by DEXA (T score < –1; Table 3). In contrast to the results using DEXA, DEQCT showed a progressive decline in BMD (mg/cm^3) with age. Multiple regression showed no significant relationship between age and DEXA T scores (r = 0.053, p = 0.7), but BMD as measured by DEQCT was significantly lower with increasing age (r = 0.244, p = 0.03).

Table 1. Patient characteristics for each disease duration in patients with AS (n = 103). Values are given as mean ± standard deviation, unless otherwise indicated.

	Group 1 (≤ 5 years), n = 27	Group 2 (5–10 years), n = 48	Group 3 (> 10 years), n = 28
Age, yrs	34.2 ± 11.8	38.1 ± 11.8	49.1 ± 11.1*†
Sex, % male	63	65	64
Disease duration, yrs	2.5 ± 1.1	7.0 ± 1.8*	19.7 ± 6.8*†
HLA-B27-positive, %	85.2	85.4	75
BASDAI	4.4 ± 2.4	5.3 ± 2.0	4.7 ± 2.2
BASFI	3.1 ± 2.5	3.3 ± 2.1	3.5 ± 2.0
CRP, mg/dl	12.8 ± 11.0	17.6 ± 17.5	13.0 ± 14.4

* Significant difference to Group 1 ($p < 0.05$); † significant difference to Group 2 ($p < 0.05$).

Table 2. Measures of bone metabolism: Mean values of alkaline phosphatase (ALP), parathyroid hormone (PTH) and desoxypyridinoline: creatinine ratio in urine (DPYR:Cr) in AS patients (n = 103), for each disease duration. Values are given as mean ± standard deviation.

	Group 1 (≤ 5 years), n = 27	Group 2 (5–10 years), n = 48	Group 3 (> 10 years), n = 28	Normal Range
ALP, U/l	109.8 ± 44.6	106.8 ± 37.8	118.2 ± 32.6	60–170
PTH, 10–65 ng/l	28.2 ± 15.3	28.9 ± 11.4	35.5 ± 12.7†	16–42
Vitamin D, ng/l	19.2 ± 11.1	18.9 ± 11.8	23.3 ± 12.2	10–65
Osteocalcin, µg/l	8.6 ± 4.3	8.8 ± 5.8	8.4 ± 7.6	4.2–8.8
DPYR:Cr, nmol/mmol	6.0 ± 1.7	5.2 ± 2.0	4.7 ± 2.2*	2.5–5.5

* Significant difference to Group 1 ($p < 0.05$); † significant difference to Group 2 ($p < 0.05$).

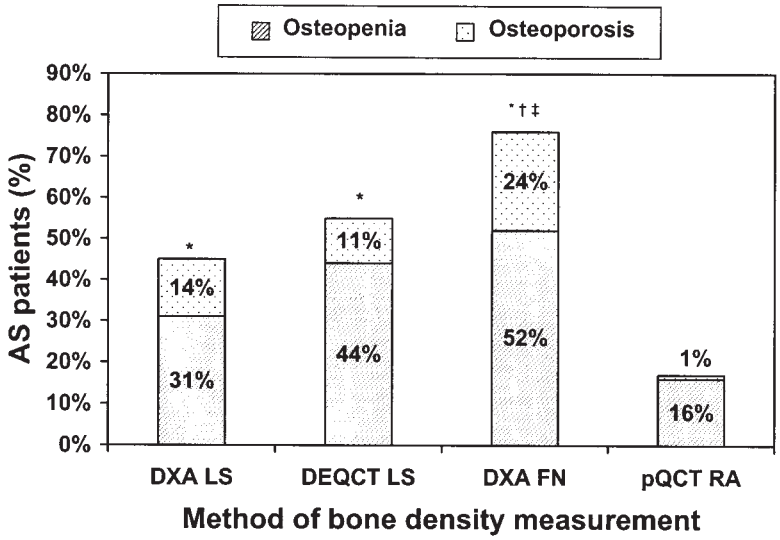

Figure 1. Comparison of the relative frequencies of osteoporosis and osteopenia at different sites in 103 patients with AS. *Proportion of patients with low bone density (osteopenia or osteoporosis) was significantly higher than pQCT RA ($p < 0.01$). †Proportion of patients with low bone density (osteopenia or osteoporosis) was significantly higher than DXA LS ($p < 0.0001$). ‡Proportion of patients with low bone density (osteopenia or osteoporosis) was significantly higher than DXA LS ($p < 0.0001$). DXA: dual-energy x-ray absorptiometry, LS: lumbar spine, DEQCT: dual-energy quantitative computed tomography, pQCT: peripheral QCT, FN: femoral neck, RA: rheumatoid arthritis.

Table 3. Mean bone density measured by different methods in AS patients (n = 103), for each disease duration. Values are given as mean ± standard deviation.

	Group 1 (≤ 5 years), n = 27	Group 2 (5–10 years), n = 48	Group 3 (> 10 years), n = 28
DEQCT, LS, mg/cm^3	116.23 ± 27.26	111.10 ± 31.87	105.22 ± 45.00
Normal > 120%			
DEXA, LS, g/cm^2	0.956 ± 0.128	0.958 ± 0.157	0.978 ± 0.157
T score, LS	–1.02 ± 0.31	–1.07 ± 0.26	–0.79 ± 0.33*†
Normal > 0			
DEXA, FN, g/cm^2	0.799 ± 0.143	0.769 ± 0.118	0.760 ± 0.121
T score, FN	–1.28 ± 0.31	–1.82 ± 0.18*	–1.69 ± 0.29*†
Normal > 0			
pQCT, RA, mg/cm^3	182.15 ± 53.14	171.75 ± 53.30	158.95 ± 52.57
Normal > 120%			

* Significant difference to Group 1 ($p < 0.05$); † significant difference to Group 2 ($p < 0.05$). T score: standard deviation below peak bone mass, LS: lumbar spine, FN: femoral neck, RA: ultra distal radius.

Table 4. Percentage (%) of AS patients (n = 103) with low bone density, grouped by the presence of syndesmophytes and disease duration.

	≤ 5 Years' Disease			5–10 Years' Disease			> 10 Years' Disease		
	Yes	No	Total	Yes	No	Total	Yes	No	Total
Syndesmophytes, n (%)	7 (26)	20 (74)	27	26 (54)	22 (46)	48	23 (82)	5 (18)	28
DEQCT at LS, mg/cm^3									
> 120	14	50	41	43	50	46	43	60	46
> 80 < 120	86	50	59	38	50	44	36	40	36
< 80	0	0	0	19	0	10	21	0	18†
DEXA at LS, T score									
> –1	29	50	44	47	64	54	64	40	60
< –1, > –2.5	71	30	41	33	27	31	36	40	36
< –2.5	0	20	15	19	10	15	0	20	4†
DEXA at FN, T score									
> –1	29	35	33	23	26	25	15	20	14
< –1, > –2.5	71	50	56	38	63	50	54	60	57
< –2.5	0	15	11	38	11*	25	31	20	29†

* Significant difference from patients with syndesmophytes ($p < 0.05$); † significant difference in trend across disease duration compared to each of the other measurement methods ($p < 0.05$). LS: lumbar spine, FN: femoral neck, T score: standard deviation below peak bone density.

At the femoral neck, the mean bone density was reduced in all groups (Table 3). All groups were osteopenic (T score < –1), and the mean T score was lowest in Group 2. There was a trend toward lower values with increasing age and disease duration, but this did not reach statistical significance ($p > 0.05$) on multiple regression.

In patients with disease duration < 5 years (n = 27), low bone density (osteopenia or osteoporosis) at the hip and the spine by DEXA was found in 67% and 56% of the patients, respectively (Table 4). In patients with a longer disease duration, > 10 years (n = 28), 29% were osteoporotic at the hip and only 4% at the lumbar spine. In contrast, spinal DEQCT found 59% of patients with early disease were osteopenic; 36% of patients with long-standing disease were osteopenic and 18% osteoporotic (Table 4). DEXA at the femoral neck classified more patients as osteoporotic with longer disease duration than both DEXA at the lumbar spine (chi-square for trend = 13.69, df = 2, p = 0.001) and DEQCT (chi-square for trend = 6.28, df = 2, p = 0.04). At the lumbar spine, DEQCT was seen to classify an increasing percentage of patients as osteoporotic with increasing disease duration, compared to a decreasing classification of osteoporosis when DEXA was used (chi-square for trend = 24.56, df = 2, $p < 0.0001$).

Using pQCT at the forearm, 85% of Group 1, 83% of Group 2, and 80% of Group 3 patients had a normal bone density. In contrast, osteopenia was found in 15%, 15%, and 20%, respectively. One patient in Group 2 had osteoporosis detected at the forearm.

There were no significant differences in the prevalence of osteopenia or osteoporosis between patients of different disease durations for any of the methods used (all $p > 0.1$).

New bone formation and bone density. Syndesmophytes were found in 54.5% of the total cohort. Mean disease dura-

tion in patients with syndesmophytes was 13.4 years, longer than in those patients without syndesmophytes (mean duration 6 years).

In Group 1 (< 5 years' disease duration), there were already 26% with syndesmophytes, and syndesmophytes were found in 55% of patients in Group 2. In Group 3, 82% of patients had syndesmophytes on radiographs.

In the presence of syndesmophytes, more patients were seen to have diminished bone density when measured by DEXA of the femoral neck or by DEQCT than by DEXA of the lumbar spine, as expected (Figure 2). In patients without syndesmophytes, DEXA of femoral neck classified more patients as osteopenic or osteoporotic than either lumbar spine measurement.

Disease duration, syndesmophyte formation, and bone density. The presence of syndesmophytes was significantly related to disease duration (chi-square = 17.51, $p < 0.0001$). The longer disease was present, the more likely that syndesmophytes were found, as shown in Table 4. Twenty-six percent of patients with disease duration < 5 years (Group 1) had already formed syndesmophytes. After 5–10 years of disease (Group 2), 55% had syndesmophytes, as did 81% of those with > 10 years of disease (Group 3). There was no relationship between syndesmophyte formation and age.

Of patients with short disease duration (5 years or less, Group 1) who already had syndesmophytes on radiographs, 86% were osteopenic at the lumbar spine as measured by DEQCT, and 71% as measured by DEXA at both lumbar spine and femoral neck. Those patients without syndesmophytes at 5 years or less were less frequently osteopenic by any method (50%, 50%, and 65%, respectively), although this trend did not show statistical significance for any method (all $p > 0.09$).

After 5–10 years of disease (Group 2), osteoporosis was seen at the lumbar spine in 19% of patients with syndesmophytes by both DEQCT and by DEXA, more than double the proportion seen in patients without syndesmophytes. DEXA at the femoral neck classified significantly more patients with syndesmophytes as osteoporotic compared to those without syndesmophytes (38% compared to 11%; chi-square = 4.028, $p = 0.04$).

Osteoporosis was more frequently detected in patients with syndesmophytes and a long disease duration (> 10 years) when both DEXA at the femoral neck and DEQCT at the lumbar spine were used to measure bone density (21% and 31%, respectively). No case of osteoporosis was identified by DEXA at the lumbar spine in this group. DEQCT did not identify any patient without syndesmophytes with osteoporosis after 10 years of disease, but DEXA at the lumbar spine identified 33% of patients at a T score < –2.5. No comparisons reached statistical significance in this group due to the infrequent occurrence of long-standing AS without syndesmophytes.

Disease activity, syndesmophyte formation, and bone density. In the entire cohort, 52% of patients had CRP > 8 and 67% a BASDAI > 4.

In 72% of the cases with an increased CRP there was also a BASDAI > 4. However, there was a similarly high percentage (62%) of patients with an increased BASDAI but a normal CRP. Chi-square testing did not show any significant association between the groups.

Disease activity indicators were increased in patients

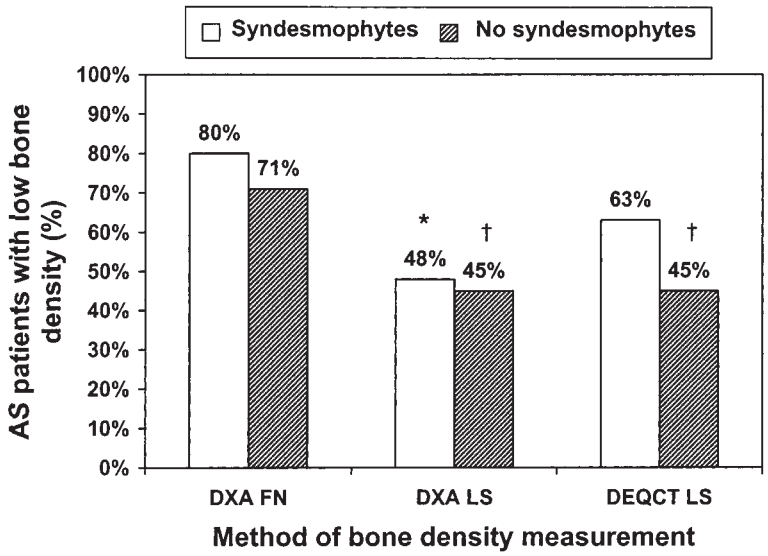

Figure 2. Relative frequency of low bone density (osteopenia or osteoporosis) in AS patients with and without syndesmophytes. *Significantly different from DXA FN with syndesmophytes (chi-square = 10.90, $p = 0.001$). †Significantly different from DXA FN without syndesmophytes (*hi-square = 5.23, $p = 0.02$). For definitions, see Figure 1 legend.

with and without syndesmophytes (Table 5). Disease activity was relatively high in most patients, independent of duration of disease. In particular, the BASDAI was elevated (> 4) in 75% of patients with more than 5 years of disease.

There was no significant relationship between bone density and BASDAI, BASFI, or CRP in patients with syndesmophytes. Seventy-eight percent of AS patients without syndesmophytes and a BASDAI > 4 had a normal bone density, whereas none had normal bone measurements if they had a BASDAI < 4. There was no correlation between the BASDAI and bone density as measured by DEQCT, but DEQCT in this group was moderately correlated with the BASFI (r = 0.386, p = 0.045). The interrelationship between bone density measured by DEXA at the femoral neck, syndesmophytes, and disease activity indicators is shown in Table 5. There was no statistically significant relationship between bone density measured at any site by any method with elevated serum CRP levels.

Bone metabolism markers. Osteocalcin levels were elevated in 34% of patients. There was no significant difference in mean osteocalcin levels between groups, as divided by disease duration (Figure 3). By 10 years of disease, most patients had normal osteocalcin levels.

Disease activity represented by the BASDAI was not significantly correlated with increased osteocalcin levels. The frequency of increased osteocalcin levels was comparable to the frequency of increased CRP levels (r = 0.22, p = 0.04). Among patients with elevated CRP (CRP > 8), 61% also had an increased osteocalcin level.

An elevated osteocalcin level was not correlated with bone density (all p > 0.2).

Elimination of deoxypyridinoline in the urine was not correlated with osteocalcin levels. Similarly, there was no statistically significant relationship between urinary deoxypyridinoline and the BASDAI score or CRP levels.

DISCUSSION

This study confirms that patients with AS already have reduced bone mineral density at the lumbar spine and the femoral neck early in the disease process. The data further indicate that patients with radiographic evidence for new bone formation are even more likely than those without syndesmophytes to develop osteoporosis at the spine and the femoral neck.

Low bone density has been well documented in patients with AS, particularly in early disease[6-12]. In established disease, 20%–60% of patients are expected to have osteopenia or osteoporosis. El Maghraoui, *et al*[10] have shown that osteoporosis and osteopenia as defined by the WHO standard occurred at the lumbar spine in 18.7%–31.2% of AS patients and at the femoral neck in 13.7%–41.2%. A French study[11] found 46.5% of AS patients had low bone density at L2–L4 and 26.8% at the femoral neck, while the incidence was much lower in control subjects (23.9% and 10%; p = 0.001 and 0.08). Our own observations were consistent with these findings. Bone density was not reduced at the radius in our study, consistent with previous research[25].

These conclusions are limited by the degree to which different modalities of BMD measurement are comparable with each other. Different machines incorporate different manufacturers' norms, and measure different aspects of bone structure and composition. The use of T scores to define osteoporosis was developed for DEXA at the hip in postmenopausal women[22], and valid arguments have been made against applying this definition to other technologies and populations[26]. Nevertheless, in the absence of large comparative studies of fracture prediction, comparisons between DEXA, DEQCT, and pQCT must be considered using available reference ranges. For clinical practice, these findings highlight the importance of interpreting BMD in AS patients with respect to the imaging methodology used and the populations used for manufacturer norms.

DEXA technology is considered the gold standard for

Table 5. Relationship of low bone density (BMD) measured by DEXA at femoral neck to BASFI, BASDAI, and CRP in patients with and without syndesmophytes.

	N (%)	BASFI > 3, %	BASDAI > 4, %	CRP > 8, %
BMD with syndesmophytes, n = 55				
Normal BMD (T score ≥ 0)	11 (20)	63	70	57
Osteopenia (T score –1 to 0)	27 (49)	45	54	53
Osteoporosis (T score < –2.5)	17 (31)	66	50	43
Normal BMD compared to osteopenia/osteoporosis		chi-square = 0.115, p = 0.73	chi-square = 0.565, p = 0.45	chi-square = 0.005, p - 0.95
BD without syndesmophytes, n = 46				
Normal BMD (T score ≥ 0)	13 (28)	75	82	53
Osteopenia (T score –1 to 0)	26 (57)	36	10	40
Osteoporosis (T score < –2.5)	7 (15)	0	0	0
Normal BMD compared to osteopenia/osteoporosis		chi-square = 4.631, p = 0.03*	chi-square = 17.063, p < 0.0001*	chi-square = 0.326, p = 0.57

* Significant (p < 0.05). T score: standard deviation below peak bone density.

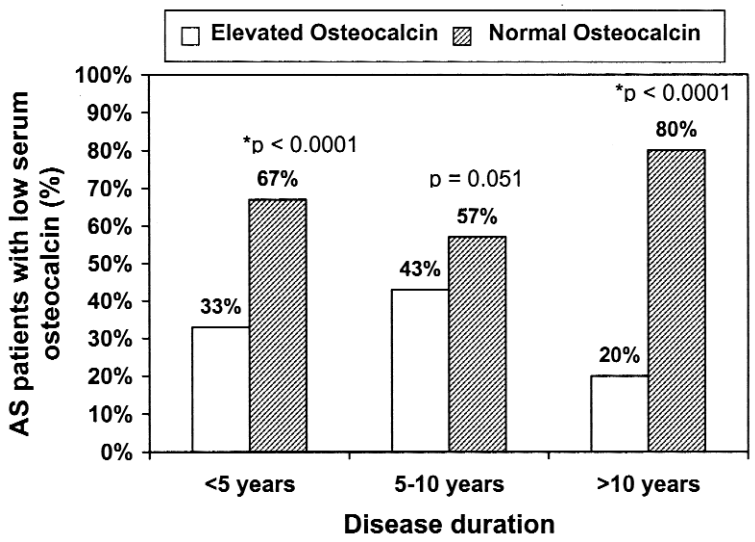

Figure 3. Proportion of patients with elevated osteocalcin levels, divided by disease duration.
*Significantly higher than in patients with syndesmophytes ($p < 0.05$).

measuring spinal bone density in involutional osteoporosis. It is, however, not as reliable in AS, as syndesmophyte formation causes falsely elevated values due to hyperossification[13,27]. In patients without substantial syndesmophytosis, DEXA measurement is more valid. This is reflected in the differing results for bone density seen previously[28] and in our cohort of AS patients dependent on the presence of syndesmophytes. Computer tomography results at the spine and DEXA at the femoral neck show acceptable correlation with each other, whereas there is no significant relationship between DEXA and another technique commonly used for determining osteoporosis, ultrasound measurement at the calcaneus[29].

The association between osteoporosis and immobility (or "disuse") is well recognized[30], and it might be that the low bone density seen in AS patients is related to spinal immobility, particularly in those individuals with significant syndesmophyte formation. Although it is an attractive theory, disuse osteoporosis is thought to be a result of reduced weight-bearing, not lack of skeletal mobility, and this is less likely to be a factor in AS patients unless the individual is sufficiently impaired to reduce daily weight-bearing activity. Liu, *et al*[31] showed that QCT is sensitive for spinal disuse osteoporosis in patients with spinal cord injury, but DEXA in the same cohort was unable to detect a significant reduction in bone density. This was not the case in our AS group, where both measurement techniques revealed increased osteopenia and osteoporosis in patients with syndesmophytes compared to those without syndesmophytes. Immobility is unlikely to be a determining factor in reduced bone density in AS.

The role of osteoblasts in new bone formation in the context of AS is incompletely defined at this time. Cross-sectional studies of serum osteocalcin in AS have had conflicting results, with most showing levels to be decreased[29,32,33] or normal[28,34,35], but not related to inflammatory markers. Recently, a case control study of patients with spondyloarthritides showed osteocalcin levels were significantly higher in AS patients than in healthy controls[36]. A short prospective study of 89 AS patients undergoing physical therapies for 3 weeks showed elevated osteocalcin levels in 26% of patients at baseline, and change in osteocalcin levels was weakly but significantly inversely associated with erythrocyte sedimentation rate (ESR)[37]. Disease duration has not been specifically addressed in such studies. In this study, we found that younger AS patients (disease duration < 10 years) and those with elevated CRP levels more frequently had elevated osteocalcin levels. This suggests that higher osteocalcin levels accompany systemic disease activity. In contrast, older patients with inactive disease mostly had lower osteocalcin levels. Considering these data together, a reliable indicator for bone formation in AS is still lacking. In contrast, studies of bone resorption markers and disease activity have shown the excretion of pyridinoline crosslinks is correlated with ESR[34,35] and CRP[10,38]. Lange, *et al*[39] showed a correlation between potential disease activity indicators [including serum tumor necrosis factor-α (TNF-α)] and markers for increased bone metabolism. These results together support the assumption that there is a phase of increased inflammatory activity in AS that leads to increased bone resorption and thus decreased bone density.

Our study was not able to show a strong relationship between BMD and either disease activity (by BASDAI) or inflammation (measured by CRP) in patients with AS. It is likely that cumulative inflammation is more important to bone than a single measure, reflecting both local and systemic inflammatory changes that over time might have influenced bone turnover.

Analogous to studies in other inflammatory conditions, it is plausible that cytokines formed during the inflammatory reaction such as TNF-α, interleukin 1ß (IL-1ß), and IL-6 cause a diffuse local osteopenia in the vertebral body[40], and simultaneously new bone formation is mediated by growth factors including transforming growth factor-ß, insulin-like growth factor, or bone morphogenetic protein[41].

Do these observations offer therapeutic strategies for bone changes in AS? To date there are no studies to answer this question. A recent study of AS patients has suggested that there may be a link between vitamin D receptor genotypes and the presence of osteoporosis[42], but there is no evidence that treating AS patients with vitamin D supplement affects bone density or fracture risk, as has been shown in involutional and postmenopausal osteoporosis[43-45]. It is not clear if calcitonin or bisphosphonates improve osteopenia in AS. Intravenous pamidronate has been shown to reduce disease activity in AS[46-48], but specific studies on bone are lacking.

Medications for prevention of vertebral fracture are not widely used in the management of AS[49]; analgesia with nonsteroidal antiinflammatory agents and regular physiotherapy make up the mainstay of treatment. There are specific indications for the use of antiinflammatory-based therapy[50,51], and recent results with the TNF-α inhibitor infliximab are promising for both disease activity[52] and improvement of bone density[53]. As we introduce new therapeutic strategies into the management of our patients with AS, it will also be imperative to address treatment of osteoporosis.

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