Femoral Bone Mineral Density Is Associated with Vertebral Fractures in Patients with Ankylosing Spondylitis: A Cross-sectional Study

JAE-BUM JUN, KYUNG-BIN JOO, MIN-YOUNG HER, TAE-HWAN KIM, SANG-CHEOL BAE, DAE-HYUN YOO, and SEONG-KYU KIM

ABSTRACT. ***Objective.*** To determine the association between vertebral fractures and clinical, laboratory, and radiological variables in patients with ankylosing spondylitis (AS).

Methods. Sixty-eight men with AS and 91 sex- and age-matched controls were consecutively enrolled. Vertebral fractures were assessed according to a visual semiquantitative grading system using plain radiographs of the lumbar spine obtained from patients with AS. Disease activity variables including C-reactive protein, erythrocyte sedimentation rate, finger-to-ground distance score, Schober's Index score, Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) score, and syndesmophyte score were identified. Assessments of bone mineral density (BMD) of the lumbar spine and the femur in patients and controls were performed using an anteroposterior dual energy x-ray absorptiometry technique.

Results. Eleven patients (16.2%) out of the total of 68 patients with AS had vertebral fractures; these were identified as wedge deformities (n = 5) or biconcave (n = 6) deformities. BMD levels of the lumbar spine and femur in patients were significantly reduced compared with those of age-matched controls. There were significant differences in the Schober's Index scores, finger-to-ground distance scores, BASRI scores of the lumbar spine, syndesmophyte scores, and intertrochanter values of BMD among AS patients both with and without vertebral fractures. Multiple logistic regression analyses revealed that intertrochanteric BMD values also were independently associated with vertebral fractures in AS ($p = 0.041$).

Conclusion. We demonstrated evidence of a correlation between low femoral BMD levels and risk of vertebral fractures in patients with AS, especially at the intertrochanteric area. Longitudinal studies in a large population are required to determine the diagnostic implications of femur BMD for increased risk of vertebral fractures in AS. (J Rheumatol 2006;33:1637–41)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS, OSTEOPOROSIS, FEMUR, BONE DENSITY, VERTEBRAL FRACTURE

Loss of bone mass (osteopenia or osteoporosis) of the spine and femur is a well recognized complication of ankylosing spondylitis (AS), even in the early stages of the disease[1,2]. It was known that patients with AS have an increased susceptibility to vertebral fractures due to secondary diffuse osteoporosis[3,4]. However, studies that evaluated the association between the values of bone mineral density (BMD) measurements and vertebral fractures in AS patients showed a lack of association between the 2 events[2,4]. The rate of vertebral fractures in AS has been estimated to range from 0.4% to 18%, according to variance of study design[2-6]. However, the clinical, laboratory, or radiological variables for predicting the risk of vertebral fractures in patients with AS have not yet been determined.

The aim of our investigation was to establish the relationship between vertebral fractures and BMD levels of the lumbar spine and femur, as well as clinical, laboratory, and radiological variables.

MATERIALS AND METHODS

Subjects. Sixty-eight men with AS were consecutively enrolled at the Hospital for Rheumatic Diseases, Hanyang University, from September 2004 to December 2004. All patients met the modified New York criteria for AS[7]. We excluded patients with hyperparathyroidism, hyperthyroidism, chronic liver disease, and/or renal insufficiency; patients who were currently taking steroids were also excluded from the study, as steroids can affect bone metabolism in the development of osteoporosis. Women with AS were excluded

From the Department of Rheumatology, The Hospital for Rheumatic Diseases, the Department of Diagnostic Radiology, Hanyang University, Seoul; and Division of Rheumatology, Department of Internal Medicine, College of Medicine, Dankook University, Cheonan, Chungcheong Nam Do, South Korea.

Supported by a grant of the research fund of Hanyang University (HY-2002-S).

J-B. Jun, MD, PhD, Associate Professor of Medicine, Department of Rheumatology, Hospital for Rheumatic Diseases; K-B. Joo, MD, PhD, Professor of Radiology, Department of Radiology, Hanyang University; M-Y. Her, MD, Clinical Fellow in Rheumatology; T-H. Kim, MD, PhD, Assistant Professor of Medicine; S-C. Bae, MD, PhD, MPH, Professor of Medicine; D-H. Yoo, MD, PhD, Professor of Medicine, Department of Rheumatology, Hospital for Rheumatic Diseases; S-K. Kim, MD, PhD, Assistant Professor of Medicine, Division of Rheumatology, Department of Internal Medicine, College of Medicine, Dankook University.

Address reprint request to Dr. S-K. Kim, Division of Rheumatology, Department of Internal Medicine, College of Medicine, Dankook University, Cheonan, Chungcheong Nam Do, 330-715, South Korea. E-mail: kimsk714@empal.com

Accepted for publication March 31, 2006.

since their normal BMD values are different from those of men, and there are no adequate data available for identifying the value of bone loss in increasing a man's risk of developing fractures. Patients with a history of traumatic injury such as falls and motor vehicle accidents were also excluded. Controls matched for sex, age, and body mass index (BMI) were recruited at the Health Promotion Center of the same hospital.

Clinical and laboratory assessments. Age, BMI (kg/m^2), and the duration of disease were retrospectively studied from the patients' medical records. Patient examinations included finger-to-ground distance and Schober's Index score in a physical assessment of spinal mobility and disease activity. C-reactive proteins (CRP; normal values < 0.8 mg/dl) and erythrocyte sedimentation rates (ESR, Westergren method; normal values < 20 mm/h) were measured to determine inflammatory activity.

Radiological assessment. We used the Picture Archiving and Communication System (PACS; Piview Startm, Infinitt Technology Co., Ltd., Seoul, Korea) to assess vertebral fractures and severity of the radiological damage in lumbar anteroposterior (AP) and lateral views. It has been shown that the PACS is advantageous because it is available at any time and provides easy or automatic control of radiological images[8]. For the imaging assessment of radiological damage, we used the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s), which is reproducible and reliable, and is a rapid radiological scoring system used in AS[9]. To conveniently assess clinical status, all patients were classified into 2 groups according to the BASRI-s scoring system (scored from 0 to 4): the mild AS group, which included patients with scores of 0–1, and the advanced AS group, which included patients with scores of 2–4[10]. Syndesmophyte scores were graded on a 0–3 scale in a plain radiograph of the lumbar spine[11]. We then classified patients into mild (score of 0) or advanced (score 1–3) groups in order to assess their clinical status.

Vertebral fractures of the lumbar spine were assessed according to a visual semiquantitative grading system[12]. Vertebral fractures were defined as a reduction of more than 20% in anterior, middle, and/or posterior height. The vertebral fracture assessments were confirmed by an experienced bone and joint radiologist (KBJ).

Bone densitometry assessment. Axial and appendicular BMD of the lumbar spine (L2–L4, posteroanterior view) and the left proximal femur (neck, intertrochanteric area, greater trochanter, and Ward's triangle) were assessed using the AP dual energy x-ray absorptiometry (DEXA) technique (QDR 4500A, Hologic Inc., Waltham, MA, USA). Observational differences between the values of 2 different DEXA observations were adjusted using 20 successive pretests of the anthropomorphic spine phantom.

Statistical analysis. Estimated values are listed as mean ± standard deviation (SD). Differences in BMD values and characteristics (including age and BMI) between AS patients and controls were assessed using an independent-samples t test. Variables including the duration of disease, finger-to-ground distance, Schober's Index, CRP, ESR, BASRI scores, and syndesmophyte scores in AS patients were assessed by descriptive analysis. Differences among variables between patients with and without vertebral fractures were also compared using t tests. These results were reassessed using a multiple logistic regression analysis to exclude the confounding effects of clinical variables on vertebral fractures in AS.

RESULTS

The basic characteristics and BMD measurements of AS patients and the controls are shown in Table 1. BMD levels of the lumbar spine and femur of AS patients were significantly lower compared with those of the controls in all investigated regions. We observed 11 patients (16.2%) with vertebral fractures. Six of these 11 patients had biconcave fractures and 5 had wedge compression fractures of the vertebrae. No significant differences were identified between the biconcave and wedge morphometric fractures in terms of the variables presented in Table 1 (data not shown).

According to the BASRI scores, there were no significant differences between the lumbar and femur BMD levels between the mild and advanced AS groups, except for the intertrochanteric area of the femur ($p = 0.017$) (Table 2). However, there were no differences between BMD levels of all the measured regions between the 2 groups, based on the syndesmophyte scores.

A negative correlation between the mean lumbar spine BMD and the serum levels of both ESR and CRP was identified (data not shown). This correlation was not observed for the femur BMD. We also found that there was a negative association between the Schober's Index and the level of CRP ($p = 0.049$).

In a comparison between AS patients both with and without vertebral fractures, there were significant differences for Schober's Index scores, finger-to-ground distance scores, BASRI scores, syndesmophyte scores, and BMD values in the intertrochanteric area of the femur (Table 3). Further, no differences between the lumbar and femur BMD values were demonstrated, irrespective of the presence of vertebral fractures, except for differences of the intertrochanteric area, disease duration, ESR, and CRP.

Multiple logistic regression analyses were performed to exclude potential influences from any of the confounding factors, including age, Schober Index score, finger-to-ground test score, BASRI score, syndesmophyte score, and BMD levels of the intertrochanteric femur showing significant differences between AS patients with fractures and patients without fractures (Table 4). Intertrochanteric BMD value appeared to be a significant factor associated with the risk of vertebral fractures ($p = 0.041$), although the statistical significance was not seen for some physical or radiological variables associated with vertebral fractures.

DISCUSSION

Vertebral fractures are one of the well known complications seen in patients with AS[2,4]. Although the prevalence of vertebral fractures remains unclear, their reported occurrence in AS varies from 0.4% to 18%[2-6]. In our study, the prevalence of vertebral fractures was estimated at 16.2%. The precise etiology or mechanism of vertebral fractures in AS has not been clearly determined. Previous studies have suggested that the majority of vertebral fractures were caused by mechanical injuries such as minor falls and motor vehicle accidents[13,14]. Recently, reduced bone mass (osteopenia or osteoporosis) was also identified as one of the variable clinical features of AS[1,2,11]. Based on this finding, it has been proposed that osteoporosis is a major determinant in the development of vertebral fractures in AS, although some studies have shown no correlation between BMD measurements and vertebral fractures[2,4].

No specific clinical or laboratory variables (except pain, stiffness, and sleep disturbance) known to be associated with radiological bone changes (including ankylosis or joint sclerosis) have been identified in AS[15]. There is an ongoing con-

Table 1. Basic characteristics of patients with ankylosing spondylitis (AS) and controls.

Variables, mean ± SD	AS, n = 68	Controls, n = 91	p
Age, yrs	30.7 ± 6.5	30.0 ± 7.0	NS
Body mass index, g/m^2	22.3 ± 3.3	23.0 ± 2.3	NS
Disease duration, mo	86.0 ± 65.0	—	—
Schober's index, cm	3.3 ± 2.2	—	—
Finger-to-ground test, cm	21.0 ± 14.7	—	—
ESR, mm/h	37.0 ± 33.7	—	—
CRP, mg/dl	2.52 ± 2.69	—	—
BASRI score of lumbar spine, 0–4	1.7 ± 1.7	—	—
Syndesmophyte score, 0–3	0.9 ± 1.1	—	—
Vertebral fracture, %	16.2*	—	—
BMD of lumbar spine, g/cm^2			
L2	0.93 ± 0.15	0.99 ± 0.10	0.005
L3	0.94 ± 0.16	1.01 ± 0.11	0.002
L4	0.97 ± 0.14	1.02 ± 0.10	0.010
BMD of femur, g/cm^2			
Neck	0.78 ± 0.13	0.87 ± 0.11	< 0.001
Greater trochanter	0.64 ± 0.10	0.71 ± 0.10	< 0.001
Intertrochanter	0.98 ± 0.16	1.15 ± 0.13	< 0.001
Ward's triangle	0.68 ± 0.17	0.98 ± 0.11	< 0.001

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASRI: Bath Ankylosing Spondylitis Radiological Index; BMD: bone mineral density; L: lumbar spine. * Eleven patients had vertebral fractures including wedge or biconcave deformities.

Table 2. Comparison of BMD between mild AS and advanced AS on the basis of radiological scoring.

Variables, mean ± SD	BASRI Score* Mild AS, n = 36	BASRI Score* Advanced AS, n = 32	p	Syndesmophyte Score† Mild AS, n = 36	Syndesmophyte Score† Advanced AS, n = 32	p
Lumbar spine, g/cm^2						
L2	0.94 ± 0.16	0.92 ± 0.13	0.447	0.94 ± 0.16	0.92 ± 0.13	0.743
L3	0.95 ± 0.15	0.93 ± 0.18	0.546	0.94 ± 0.15	0.94 ± 0.17	0.992
L4	0.95 ± 0.14	0.99 ± 0.15	0.198	0.94 ± 0.14	1.00 ± 0.14	0.066
Femur, g/cm^2						
Neck	0.80 ± 0.13	0.77 ± 0.13	0.326	0.78 ± 0.12	0.78 ± 0.14	0.989
Greater trochanter	0.66 ± 0.10	0.62 ± 0.10	0.104	0.65 ± 0.10	0.63 ± 0.12	0.648
Intertrochanter	1.02 ± 0.16	0.93 ± 0.15	0.017	1.00 ± 0.15	0.95 ± 0.16	0.159
Ward's triangle	0.70 ± 0.17	0.65 ± 0.17	0.223	0.69 ± 0.15	0.67 ± 0.19	0.669

BMD: bone mineral density; SD: standard deviation; L: lumbar spine. * Mild (0–1) and advanced (2–4) AS were classified according to BASRI scores (0–4). † Mild (0) and advanced (1–3) AS were classified according to syndesmophyte scores (0–3).

flict of opinions about an association between BMD levels and disease activity variables such as ESR, CRP, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Toussirot, *et al* failed to identify relationships between disease activity measurements (ESR, CRP, and BASDAI) and BMD levels[16]. In contrast, a reduced lumbar spine BMD was also detected in AS patients with higher levels of ESR or CRP[17]. With the inclusion of ESR and CRP measurements in our study, we also confirmed that there was a significant negative correlation between BMD levels of the lumbar spine and acute phase reactants (ESR and CRP), but not with BMD levels of the femur. However, the association between BMD levels and diverse disease activity variables such as BASRI, ESR, and CRP should be determined in larger studies.

A previous study proposed the limitations of using only lumbar spine BMD measurement to predict the risk of vertebral fractures in AS patients[2-4]. In this study, we also failed to identify a correlation between vertebral fractures and lumbar BMD levels. Calcified paravertebral structures such as syndesmophytes and calcification of ligaments interfere with accurate measurement of lumbar BMD by AP DEXA. If measurements of lumbar BMD are assessed by AP DEXA, potential for overestimation for lumbar BMD in AS patients remains. Despite this weakness of AP lumbar DEXA, we identified lumbar BMD levels in AS patients that were lower than in controls. Quantitative computed tomography or a lateral projection of the lumbar spine by DEXA reflecting more accurate results than AP lumbar DEXA in determining the

Table 3. Comparison of characteristics between patients with ankylosing spondylitis (AS) with or without vertebral fractures.

Variables, mean ± SD	AS without Vertebral Fractures, n = 57	AS with Vertebral Fractures, n = 11	p
Age, yrs	30.2 ± 6.6	33.3 ± 5.7	0.153
Body mass index, g/m^2	22.3 ± 3.4	22.5 ± 2.8	0.854
Disease duration, mo	81.2 ± 63.4	110.4 ± 70.6	0.176
Schober's index, cm	3.6 ± 2.2	1.9 ± 1.2	0.001
Finger-to-ground test, cm	18.9 ± 14.4	31.6 ± 11.1	0.007
ESR, mm/h	37.9 ± 34.1	32.6 ± 32.6	0.632
CRP, mg/dl	2.7 ± 2.8	1.7 ± 2.1	0.250
BASRI score of lumbar spine, 0–4	1.3 ± 1.6	3.3 ± 1.3	< 0.001
Syndesmophyte score, 0–3	0.7 ± 1.0	1.6 ± 1.0	0.007
BMD of lumbar spine, g/cm^2			
L2	0.94 ± 0.15	0.90 ± 0.11	0.505
L3	0.95 ± 0.17	0.92 ± 0.14	0.625
L4	0.96 ± 0.15	1.00 ± 0.11	0.424
BMD of femur, g/cm^2			
Neck	0.79 ± 0.13	0.71 ± 0.08	0.065
Greater trochanter	0.64 ± 0.11	0.64 ± 0.07	0.955
Intertrochanter	1.00 ± 0.16	0.85 ± 0.12	0.007
Ward's triangle	0.70 ± 0.17	0.59 ± 0.15	0.075

BMD: bone mineral density; SD: standard deviation; L: lumbar spine; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASRI: Bath Ankylosing Spondylitis Radiological Index.

Table 4. Multiple logistic regression analysis for cofactors that affect vertebral fractures in ankylosing spondylitis.

Cofactors	Presence of Vertebral Fractures	
	Beta	p_{adj}
Age, yrs	0.091	0.405
Schober index, cm	0.493	0.243
Finger-to-ground test, cm	0.025	0.555
BASRI score of lumbar spine, 0–4	0.676	0.277
Syndesmophyte score, 0–3	0.526	0.500
BMD of femur, g/cm^2		
Intertrochanter	–10.792	0.041

p_{adj}: adjusted p value was calculated by analysis between vertebral fractures and cofactors including age, Schober distance, finger-to-ground distance, lumbar BASRI scores, lumbar syndesmophyte scores, and intratrochanteric femoral BMD.

bone mass in AS has been suggested[18,19]. Additional studies examining the accuracy of these new methods for determining BMD measurements of the lumbar spine are required.

It has been generally accepted that there are no significant differences in lumbar or femur BMD levels in AS patients with fractures compared to those without fractures. However, in our study, we observed differences in intertrochanteric femur BMD level, clinical variables such as Schober's Index, finger-to-ground distance, and radiological scoring systems for AS including BASRI scores and syndesmophyte scores, between the AS patients with and those without fractures. Until now, no correlations between vertebral fractures and BMD levels of the lumbar or femur bones have been observed[2,4]. However, Donnelly, *et al* suggested the possibility that the reduced femur neck BMD level might help to identify the risk of vertebral fractures, even though their observations did not reach statistical significance[4]. Our study determined that intertrochanteric BMD levels were associated with vertebral fractures using a multiple logistic regression analysis, although statistical significance for other clinical or radiological variables was not observed. Our study shows that BMD level of femur offered more accurate results than that of lumbar spine in determining the bone mass in patients with AS. In addition to lumbar spine fracture, cervical and/or thoracic spine fractures have also been identified in patients with AS. However, it seems that assessment of only lumbar spine fracture is also a limitation of our study, although previous studies did not assess spinal fractures from cervical to lumbar spine[2,4].

Our results suggest that measurement of femur BMD may provide useful information to predict the risk of vertebral fractures in patients with AS, but not in all investigated regions of the femur. Larger studies are required to determine the diagnostic implications of femur BMD measurement for increased risk of vertebral fracture in AS.

REFERENCES

1. Will R, Palmer R, Bhalla AK, Ring F, Calin A. Osteoporosis in early ankylosing spondylitis: a primary pathological event? Lancet 1989;2:1483-5.
2. 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 Oxford 2000;39:85-9.
3. Ralston SH, Urquhart GD, Brzeski M, Sturrock RD. Prevalence of

vertebral compression fractures due to osteoporosis in ankylosing spondylitis. BMJ 1990;300:563-5.
4. 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.
5. 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.
6. Vosse D, Feldtkeller E, Erlendsson J, Geusens P, van der Linden S. Clinical vertebral fractures in patients with ankylosing spondylitis. J Rheumatol 2004;31:1981-5.
7. Van der Linden SM, 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.
8. Strickland NH. PACS (Picture Archiving and Communication Systems): Filmless radiology. Arch Dis Child 2000;83:82-6.
9. MacKay K, Mack C, Brophy S, Calin A. The Bath Ankylosing Spondylitis Radiology Index (BASRI): a new, validated approach to disease assessment. Arthritis Rheum 1998;41:2263-70.
10. Capaci K, Hepguler S, Argin M, Tas I. Bone mineral density in mild and advanced ankylosing spondylitis. Yonsei Med J 2003;44:379-84.
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. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
13. Hunter T, Dubo HI. Spinal fractures complicating ankylosing spondylitis. A long-term followup study. Arthritis Rheum 1983;26:751-9.
14. Hunter T, Dubo H. Spinal fractures complicating ankylosing spondylitis. Ann Intern Med 1978;88:546-9.
15. 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.
16. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology Oxford 2001;40:882-8.
17. Dos Santos FP, Constantin A, Laroche M, et al. Whole body and regional bone mineral density in ankylosing spondylitis. J Rheumatol 2001;28:547-9.
18. Lee YS, Schlotzhauer T, Ott SM, et al. Skeletal status of men with early and late ankylosing spondylitis. Am J Med 1997;103:233-41.
19. 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.