

Whole Body and Regional Bone Mineral Density in Ankylosing Spondylitis

FERNANDO PIMENTEL DOS SANTOS, ARNAUD CONSTANTIN, MICHEL LAROCHE, FABIENNE DESTOMBES, JACQUES BERNARD, BERNARD MAZIÈRES, and ALAIN CANTAGREL

ABSTRACT. Objective. To study the regional distribution of bone mass and look for factors leading to bone loss in ankylosing spondylitis (AS).

Methods. Thirty-nine patients, all men, aged 20 to 55 years and presenting with AS were studied. Four hundred sixteen gendarmes, all men aged 20 to 55 years, formed an age matched control population used to define standard values for bone mineral density (BMD) in men. The patients with AS and the controls underwent measurement of whole body BMD and regional BMD by dual-energy x-ray absorptiometry.

Results. AS was associated with spinal bone loss, with lumbar spine BMD (LSBMD) 1.085 ± 0.178 g/cm² in the AS group compared with 1.232 ± 0.136 g/cm² in the control group ($p < 0.01$). Whole body BMD and regional BMD of head, whole spine, pelvis, and legs were reduced, although this was not statistically significant. Using standard values for LSBMD from the controls, we found that 46% (18/39) of patients with AS had Z score < -1.5 SD. Biological markers of disease activity were higher in the subgroup of patients with low LSBMD than in the subgroup with normal LSBMD, with an erythrocyte sedimentation rate of 29.4 ± 23.4 mm/h versus 12.1 ± 10.8 mm/h ($p < 0.05$) and C-reactive protein at 24.8 ± 18 mg/l versus 12.7 ± 14.2 mg/l ($p < 0.05$).

Conclusion. AS is associated with bone loss, mainly concerning the lumbar spine, in patients whose disease is biologically most active. (J Rheumatol 2001;28:547-9)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS

BONE MASS

BODY COMPOSITION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder, characterized by early involvement of the sacroiliac joints, by syndesmophyte formation, and by ankylosis of the posterior interapophyseal joints. Paradoxically, AS is accompanied by increased risk of vertebral fractures^{1,2}. These vertebral fractures complicating the disease reflect spinal bone loss²⁻⁶. We studied the regional distribution of bone mass to seek factors leading to bone loss in AS.

MATERIALS AND METHODS

Patients. Thirty-nine outpatients at a rheumatology unit in southwest France were included in the study. They were all male, white, aged 20 to 55 years, and fulfilled the modified New York criteria for the diagnosis of AS⁷. We excluded patients with histories of severe endocrine, liver or kidney disorders, chronic inflammatory bowel disease, or alcohol or tobacco abuse. We also excluded patients who had received > 1 g total prednisone equivalent, as well as those whose thoracolumbar spine radio-

graphs showed syndesmophytes or ankylosis of the posterior interapophyseal joints, as these could falsify measurement of spinal bone mass.

Controls. Thirty-nine age matched men from the same area of France made up the control group. They were part of a control population of 416 gendarmes, all healthy volunteers, male, white, aged 20 to 55 years, that had served to define standard values of bone mass for men in France⁸.

Methods. At study entry, patients with AS underwent clinical examination with determination of the duration of morning stiffness by eliciting a verbal response, Schober index, and chest expansion. Laboratory assessments included measurement of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, calcium, phosphorus, total alkaline phosphatase, osteocalcin (by radioimmunoassay, RIA; Brahms Diagnostica GmbH, Hennigsdorf, Germany), 25-hydroxyvitamin D (25-OHD), and intact parathyroid hormone (PTH) (RIA; Sorin, Antony, France). Frontal pelvic radiographs and frontal and lateral radiographs of the thoracolumbar spine were routinely obtained.

In the patients with AS and controls, body composition was measured by dual energy x-ray absorptiometry (DEXA) using a Lunar DPX (Lunar Radiation, Madison, WI, USA)⁹. The variables studied were whole body BMD (WBBMD) and regional BMD of head, arms, whole spine, lumbar spine (LSBMD), pelvis and legs, bone mineral content (BMC), fat mass and lean mass. Calcium intake and physical and sporting activity were assessed by questionnaires in both groups.

Statistics. Quantitative results were expressed as means \pm standard deviation (SD). The main demographic characteristics of the AS group and controls (age, weight, height) were compared using Student's t test. Comparison of the various variables of body composition in the AS group and controls was by logistic discriminant multivariate analysis with age, weight, and height as discriminant variables, to take into account the weight difference between the 2 groups. Comparison of the main characteristics of the AS subgroups with normal or low BMD was by Mann-Whitney test. Differences were considered statistically significant at $p < 0.05$.

From the Department of Rheumatology, HGO Almada, Lisbon, Portugal; the Department of Rheumatology, CHU Rangueil, Rangueil; and Department of Medicine, CHA Larrey, Toulouse, France.

F. Pimentel dos Santos, MD, Department of Rheumatology, HGO Almada; A. Constantin, MD; M. Laroche, MD; F. Destombes, MD; B. Mazières, Professor; A. Cantagrel, Professor, Department of Rheumatology, CHU Rangueil; J. Bernard, MD, Department of Medicine, CHA Larrey.

Address reprint requests to Dr. A. Constantin, Service de Rhumatologie, CHU Rangueil, 1 avenue J. Poulhès, 31403 Toulouse Cedex 4, France. E-mail: constant@cict.fr

Submitted January 27, 2000 revision accepted September 7, 2000.

RESULTS

The main characteristics of the AS group and controls are shown in Table 1. The subjects in the control group were heavier than those in the AS group (75.6 ± 10.4 vs 69.3 ± 12.1 kg; $p < 0.05$). In the AS group, there were clinical and biological signs of disease activity: mean morning stiffness > 1 h and mean CRP 18.6 ± 16.2 mg/l. Mean values of serum creatinine, calcium and phosphorus, serum markers of bone formation, PTH, and 25-OHD were within the laboratory norms. There was no significant difference in calcium intake or physical and sporting activity between the 2 groups, although the latter tended to be higher in the control group.

The main body composition variables in the 2 groups are shown in Table 2. Lean mass, fat mass, and BMC were similar in both groups. LSBMD was lower in patients with AS than in controls (1.085 ± 0.178 vs 1.232 ± 0.136 g/cm²; $p < 0.01$). WBBMD and regional BMD of head, whole spine, pelvis, and legs were reduced in AS patients, although this was not statistically significant. Using French standard values for LSBMD in men from an age matched control population⁸, we divided the AS patients into 2 subgroups: patients with normal LSBMD (Z score ≥ -1.5 SD) and patients with low LSBMD (Z score < -1.5 SD) (Table 3). We chose this threshold to get 2 subgroups with comparable sizes. Then, according to this threshold, 54% (21/39) of AS patients had normal LSBMD and 46% (18/39) had low LSBMD. The subjects in the subgroup with normal LSBMD were heavier than those with low LSBMD (74 ± 12.4 vs 64.4 ± 9.4 kg; $p < 0.05$). Disease duration, clinical variables, calcium intake, and physical activity were similar in both subgroups. However, biological markers of disease activity

Table 1. Demographic, clinical, and biological characteristics of the ankylosing spondylitis group and the control group. Results are expressed as means \pm SD. The demographic characteristics of the AS group and the control group were compared using Student's t test.

	AS, n = 39	Controls, n = 39	p
Age, yrs	37.6 \pm 9.1	37.6 \pm 9	NS
Weight, kg	69.3 \pm 12.1	75.6 \pm 10.4	< 0.01
Height, cm	172.5 \pm 7.7	174.4 \pm 4.5	NS
Duration of disease, yrs	8.4 \pm 6.3	—	—
Morning stiffness, h	1.13 \pm 1.08	—	—
Schober index, cm	3 \pm 1.3	—	—
Chest expansion, cm	4.5 \pm 2	—	—
ESR, mm/h	20.6 \pm 20.2	—	—
CRP, mg/l	18.6 \pm 16.2	—	—
Serum calcium, mmol/l	2.35 \pm 0.09	—	—
Serum phosphorus, mmol/l	1.05 \pm 0.18	—	—
Osteocalcin, ng/ml	8.5 \pm 3.6	—	—
Alkaline phosphatase, IU/l	89.9 \pm 26.6	—	—
25-hydroxyvitamin D, ng/ml	21.6 \pm 12.8	—	—
Parathyroid hormone, pg/ml	29.8 \pm 21.3	—	—
HLA-B27 phenotype	31/39	—	—
Physical and sporting activity, h/wk	1 \pm 1	2 \pm 2	NS

Table 2. Body composition of the AS group and the control group. Results are expressed as means \pm SD. The various quantitative data of the AS group and the control group were compared using logistic discriminant multivariate analysis with age, weight, and height as discriminant variables.

	AS, n = 39	Controls, n = 39	p
Whole body BMD, g/cm ²	1.187 \pm 0.117	1.232 \pm 0.108	NS
Head BMD, g/cm ²	2.059 \pm 0.199	2.124 \pm 0.226	NS
Arms BMD, g/cm ²	0.987 \pm 0.097	0.967 \pm 0.091	NS
Whole spine BMD, g/cm ²	1.072 \pm 0.146	1.176 \pm 0.131	NS
Lumbar spine BMD, g/cm ²	1.085 \pm 0.178	1.232 \pm 0.136	< 0.01
Pelvis BMD, g/cm ²	1.145 \pm 0.174	1.255 \pm 0.139	NS
Legs BMD, g/cm ²	1.299 \pm 0.136	1.352 \pm 0.126	NS
Fat mass, g	11610 \pm 5884	16460 \pm 6138	NS
Lean mass, g	55201 \pm 6523	58588 \pm 4957	NS
Bone mineral content, g	2966 \pm 500	3165 \pm 420	NS

were higher in the subgroup with low LSBMD than in the subgroup with normal LSBMD (ESR 29.4 ± 23.4 vs 12.1 ± 10.8 mm/h, $p < 0.05$; and CRP 24.8 ± 18 vs 12.7 ± 14.2 mg/l, $p < 0.05$).

DISCUSSION

Our results indicate that AS is associated with bone loss, mainly concerning the lumbar spine. AS does not affect the main body composition variables such as BMC, lean mass, or fat mass. The patients with low LSBMD were those with the most biologically active disease.

Spinal bone loss has already been observed by bone densitometry in patients with early AS^{2,3,5,6}. However, in advanced AS, characterized by syndesmophytes and ankylosis, spinal bone mass appears to be normal^{2,3,6} or increased⁴. Such overestimation of spinal bone mass in advanced AS should not mask the existence of trabecular bone loss. Indeed, quantitative computer tomography scan confirms spinal bone loss that is proportional to the duration of the disease^{3,6}.

In our study, bone loss was only significant at the lumbar spine. However, WBBMD and regional BMD of head, whole spine, pelvis, and legs were reduced, although this was not statistically significant. This trend toward generalized bone loss in AS is consistent with studies that have shown reduced bone mass at the femoral neck^{2,5,10,11} and legs¹¹.

Our control population of 416 gendarmes had served to define standard values of WBBMD and regional BMD for 5 year age groups from 20 to 55 years in France⁸. This control population may not be representative of the normal population since they are selected individuals from a specific occupation. Using standard values for LSBMD from this age matched control group, we found that 46% of patients with AS had Z score < -1.5 SD. The main characteristic of this subgroup of patients with low LSBMD was a greater biological activity of AS.

Table 3. Demographic, clinical, and biological characteristics of the subgroups of AS patients with normal and low BMD of the lumbar spine. Using standard values for lumbar spine BMD (LSBMD) from an age matched control population, we divided the patients with AS into 2 subgroups: patients with normal LSBMD (Z score ≥ -1.5 SD) and patients with low LSBMD (Z score < -1.5 SD). Results are expressed as means \pm SD. The 2 subgroups were compared by Mann-Whitney test.

	Normal LSBMD, n = 21	Low LSBMD, n = 18	p
Age, yrs	37.9 \pm 9.7	37.1 \pm 8.4	NS
Weight, kg	74 \pm 12.4	64.4 \pm 9.4	< 0.05
Height, cm	174.1 \pm 8.8	171.9 \pm 5.8	NS
Disease duration, yrs	8.8 \pm 6.8	8.1 \pm 5.8	NS
Morning stiffness, h	1.11 \pm 1.13	1.17 \pm 1.03	NS
Schober index, cm	3.1 \pm 1.3	2.9 \pm 1.4	NS
Chest expansion, cm	4.3 \pm 2.1	4.7 \pm 2	NS
Physical and sporting activity, h/wk	1 \pm 1	1 \pm 1	NS
ESR, mm/h	12.1 \pm 10.8	29.4 \pm 23.4	< 0.05
CRP, mg/l	12.7 \pm 14.2	24.8 \pm 18	< 0.05
Serum calcium, mmol/l	2.37 \pm 0.11	2.33 \pm 0.06	NS
Serum phosphorus, mmol/l	1 \pm 0.17	1.1 \pm 0.19	NS
Osteocalcin, ng/ml	8.6 \pm 3.1	8.2 \pm 4.8	NS
Alkaline phosphatase, IU/l	82.4 \pm 19.5	96.9 \pm 31.4	NS
25-hydroxyvitamin D, ng/ml	23.2 \pm 12.8	22.2 \pm 14	NS
Parathyroid hormone, pg/ml	32.3 \pm 25.6	25.3 \pm 15.3	NS
LSBMD, g/cm ²	1.221 \pm 0.107	0.919 \pm 0.091	< 0.0001

The pathophysiology of the axial bone loss observed in AS is still debated. Certain investigators have observed increased biochemical markers of bone resorption, particularly in patients with the most severe biological inflammatory syndromes^{10,12}. Other authors have observed decreased biochemical markers of bone formation or mineralization^{13,14}. Our study suggests that axial bone loss observed in the course of AS could be secondary to elevated levels of cytokines such as interleukin 6 (IL-6), which activate the pathways of both inflammation and bone resorption. This hypothesis seems to be confirmed by a recent study that showed elevated serum levels of IL-6 in patients with AS. The elevated IL-6 levels correlated with the clinical and biological activity of the disease and also with spinal bone loss¹⁵.

In summary, AS is associated with bone loss, mainly concerning the lumbar spine, which affects the patients whose disease is biologically most active.

REFERENCES

- Ralston SH, Urquhart GDK, Brzeski M, Sturrock RD. Prevalence of vertebral compression fractures due to osteoporosis in ankylosing spondylitis. *BMJ* 1990;300:563-5.
- Donnelly S, Doyle DV, Denton A, Rolfe J, McCloskey EV, Spector TD. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Ann Rheum Dis* 1994;53:117-21.
- 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.
- Reid DM, Nicoll JJ, Kennedy NSJ, Smith MA, Tothill P, Nuki G. Bone mass in ankylosing spondylitis. *J Rheumatol* 1986;13:932-5.
- Will R, Palmer R, Bhalla AK, Ring F, Calin A. Osteoporosis in early spondylitis: a primary pathological event? *Lancet* 1989;2:1483-5.
- Lee YSL, Schlotzhauer T, Ott SM, et al. Skeletal status of men with early and late ankylosing spondylitis. *Am J Med* 1997;103:233-41.
- 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.
- Zabraniecki L, Constantin A, Pignon A, Yvert J-P, Fournié B, Bernard J. Densité osseuse chez l'homme sain en France. Etude prospective sur 416 gendarmes [abstract] [Male bone density in France. Prospective study of 416 gendarmes]. *Rev Rhum* 1998;65:775.
- Haarbo J, Gotfredsen A, Hassager C, Christiansen C. Validation of body composition by dual energy X-ray absorptiometry. *Clin Physiol* 1991;11:331-41.
- 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.
- Mullaji AB, Upadhyay SS, Ho EKW. Bone mineral density in ankylosing spondylitis. DEXA comparison of control subjects with mild and advanced cases. *J Bone Joint Surg* 1994;76B:660-5.
- Toussiot 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.
- 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.
- Szejnfeld VL, Monier-Faugere MC, Bogner BJ, Ferraz MB, Malluche HH. Systemic osteopenia and mineralization defect in patients with ankylosing spondylitis. *J Rheumatol* 1997;24:683-8.
- Gratacós J, Collado A, Pons F, et al. Significant loss of bone mass in patients with early, active ankylosing spondylitis. A followup study. *Arthritis Rheum* 1999;42:2319-24.