

# Prevalence of Vertebral Fractures by Semiautomated Morphometry in Patients with Ankylosing Spondylitis

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**ABSTRACT. Objective.** Ankylosing spondylitis (AS) is a chronic inflammatory disease mainly affecting the axial skeleton and characterized by ossification of the spinal disc, joints, and ligaments leading to progressive ankylosis. Vertebral osteoporosis is a recognized feature of AS. Studies have confirmed a moderate to high prevalence of vertebral fractures with extremely varying ranges in patients with AS. Our objective was to estimate the prevalence of vertebral fractures in a representative Spanish population of patients with AS using a validated semiquantitative method, MorphoXpress®.

**Methods.** Patients were randomly selected from the 10 initial participating centers of the Spanish National Registry of Spondyloarthropathies (REGISPONSER) by consecutive sampling. All patients fulfilled the New York modified criteria for AS and had a baseline thoracolumbar radiograph. A prevalent vertebral fracture was defined according to the Genant classification criteria.

**Results.** The estimated prevalence of vertebral fractures was 32.4% (95% CI 25.5%–39.3%). The majority of fractures were localized in the thoracic segment (n = 100; 82.%) and were mild (n = 79; 64.8%). In logistic regression analysis, age (odds ratio per year 1.05, 95% CI 1.03–1.08,  $p < 0.001$ ), disease duration (OR per year 1.03, 95% CI 1.01–1.06,  $p = 0.011$ ), Bath Ankylosing Spondylitis Functional Index score (OR per score 1.16, 95% CI 1.03–1.30,  $p = 0.015$ ), Bath Ankylosing Spondylitis Radiographic Index-TS (OR per score 1.25, 95% CI 1.12–1.39,  $p < 0.001$ ), and wall-occiput distance (OR per cm 1.15, 95% CI 1.08–1.23,  $p < 0.001$ ) were all associated with prevalent fracture.

**Conclusion.** Semiquantitative methods are needed to improve the diagnosis of vertebral fractures in AS in order to start early treatment and to avoid complications arising from osteoporosis. (First Release March 1 2011; J Rheumatol 2011;38:893–7; doi:10.3899/jrheum.100851)

## Key Indexing Terms:

ANKYLOSING SPONDYLITIS  
MORPHOMETRY

OSTEOPOROSIS

VERTEBRAL FRACTURES  
BONE MINERAL DENSITY

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Accepted for publication December 13, 2010.

Ankylosing spondylitis (AS) is a chronic inflammatory disease mainly affecting the axial skeleton and it is characterized by ossification of the spinal discs, joints, and ligaments, leading to progressive ankylosis. AS has a prevalence of 0.1% to 1.4% in Caucasian populations and it is associated with the HLA-B27 antigen in over 90% of the cases<sup>1,2</sup>. It usually affects young men and it is diagnosed in the second or third decade of life.

Vertebral osteoporosis is a recognized feature of AS<sup>3,4</sup>, the prevalence varying widely from 19% to 62%<sup>5,6</sup>. Studies have confirmed a moderate to high prevalence of vertebral fractures in AS, yet with extremely varying ranges, from 0.4% to 18%<sup>7,8,9,10,11</sup>. This large variation between studies could probably reflect differences in the design and in patient selection and above all, differences in the definition of vertebral fracture. In spite of this, there is no disagreement that vertebral fractures have serious clinical consequences in patients with AS, as they aggravate spine deformity and lead to severe complications.

Diagnosing or ascertaining cases of vertebral fractures is not an easy task. Defining vertebral fracture by means of qualitative methods is subject to great variability. Therefore,

different quantitative and semiquantitative morphometry methods have been developed. These methods rely on 6 or more points, positioned over the margins of each vertebra from T5 to L4, used to calculate anterior, medial, and posterior heights, which makes them more reproducible<sup>12</sup>. Some studies published after the appearance of these new methods suggest a high prevalence of vertebral fractures in patients with AS<sup>9,13</sup>.

The prevalence of osteoporosis is not constant from country to country, in probable relation to differences in diet, genetics, and sun exposure. In Spain, some studies show the same variability in bone mineral density (BMD) in AS patients as in other settings<sup>14,15,16</sup>, and there is no published information on the prevalence of vertebral fractures. Given the variability in estimates, we believe a study on a truly representative sample of patients with AS is warranted. Our aim was to estimate the prevalence of vertebral fractures in representative Spanish patients with AS using a validated semiquantitative method, MorphoXpress<sup>®</sup> (developed by ImageMetrics plc, Cheshire, UK, and Procter & Gamble, Rome, Italy). In addition, we wanted to analyze the association between clinical expressions of AS and prevalent fractures.

## MATERIALS AND METHODS

We carried out a multicenter cross-sectional study. Patients were randomly selected from the 10 initial participating centers of the Spanish National Registry of Spondyloarthropathies (REGISPONER)<sup>17,18,19</sup>. Patients in REGISPONER are selected if they fulfill the European Spondylarthropathy Study Group criteria for spondyloarthritis<sup>20</sup> by consecutive sampling from patients attending the participating clinics. Patients in this study additionally fulfil the New York modified criteria for AS<sup>21</sup>. In REGISPONER, all patients have a baseline spinal radiographic examination. For this study, after randomization we excluded any patient for whom the quality of radiographs was poor or in whom one of the 2 portions of the spine was not available in radiographs.

**Case definition.** Lateral thoracolumbar radiological studies of selected patients were sent by each center, as digital radiography on a compact disk or as original radiographs, to a central reference facility at a rheumatology department in a tertiary hospital.

All radiographs were analyzed and processed by the same investigator using MorphoXpress<sup>®</sup>, a semiautomated software package applicable to radiographs<sup>22</sup>. Original vertebral radiographs were digitized. Then the operator manually targeted the centers of the upper and lower vertebrae (T7 to L5) to initialize the analysis. The software automatically finds the landmarks for a standard 6-point morphometry measurement.

The reproducibility of the MorphoXpress semiautomated method was proven in a large multicenter trial by nonradiologists<sup>22</sup>. The results of this study suggest that a non-expert radiologist can use MorphoXpress to achieve a good inter- and intra-operator reproducibility.

A prevalent vertebral fracture was defined as any reduction larger than approximately 20% in the anterior, middle, or posterior vertebral height. Fractures were then categorized as Grade 1, 2, or 3 using the Genant semiquantitative method<sup>23</sup>, which classifies fractures as mild, moderate, or severe depending on a height ratio decrease of 20%–25%, 25%–35%, or > 35%, respectively.

**Other variables and measures.** Besides vertebral fractures, the following variables were analyzed in relation to the prevalence of vertebral fractures: age, sex, time of the onset of AS, calendar year of diagnosis, and duration of the disease. For the evaluation of disease status we included the Bath

Ankylosing Spondylitis Disease Activity Index (BASDAI)<sup>24</sup> and the Bath Ankylosing Spondylitis Functional Index (BASFI)<sup>25</sup>. Damage was assessed by the Bath Ankylosing Spondylitis Radiographic Index (BASRI)<sup>26</sup> and quality of life by the Ankylosing Spondylitis Quality of Life (AsQoL)<sup>27</sup>. We additionally analyzed the influence of vertebral fractures on spinal mobility by the following measures: wall-occiput distance, the modified Schober test, thoracic expansion, and finger-floor distance.

**Statistical analysis.** We estimated the prevalence of fractures with 95% confidence intervals (CI) in AS and by gender. The sample was described in terms of proportions, means and medians, depending on the distribution of the descriptive variables. Differences in the distribution of variables between sexes were analyzed by Student t test or chi-square test. Logistic regression was used to analyze the association of variables with prevalent fracture, in both bivariate and multivariate models. The relation of fracture and gender was explored in additive models. All analyses were performed with the Stata 9.0 software (Stata Corp., College Station, TX, USA).

## RESULTS

We drew a random sample of 230 patients; however, only 176 could be included in the analysis after application of the selection criteria. Three patients were excluded for not fulfilling the New York criteria, 41 because radiographs of one of the 2 portions of the spine were not available, and 10 due to the poor quality of the images. The final sample is closely representative of the average AS patient in Spain (Table 1): a male, under age 50 years, in his late twenties when diagnosed, and with moderate disease activity and severity.

The estimated prevalence of vertebral fractures in AS, as measured by semiquantitative methods, was 32.4% (95% CI 25.5%–39.3%). The majority of vertebral fractures were localized in the thoracic segment (n = 100; 82.0%), and were mild (n = 79; 64.8%) according to the Genant classification (Table 2). Regarding the number of fractures per patient, 32 (56.1%) patients had one fracture, 17 (29.82%) had 2 fractures, and 15 (26.3%) had more than 2 fractures (Table 3).

By bivariate logistic regression, the following characteristics were all associated with prevalent fracture: age [odds ratio (OR) per year 1.05, 95% CI 1.03–1.08, p < 0.001], disease duration (OR per year 1.03, 95% CI 1.01–1.06, p = 0.011), BASFI (OR per score 1.16, 95% CI 1.03–1.30, p = 0.015), BASRI-TS (OR per score 1.25, 95% CI 1.12–1.39, p < 0.001), BASRI-T (OR per score 1.22, 95% CI 1.11–1.34, p < 0.001), and wall-occiput distance (OR per cm 1.15, 95% CI 1.08–1.23, p < 0.001). Female sex (OR 0.25, 95% CI 0.09–0.68, p = 0.007), modified Schober test result (OR per cm 0.74, 95% CI 0.60–0.92, p = 0.007), and thoracic expansion (OR per cm 0.78, 95% CI 0.65–0.93, p = 0.007) were inversely associated with prevalent fracture. In multivariate analysis, only age was an independent predictor of fractures (OR 1.05, 95% CI 1.01–1.09, p = 0.027) (Table 4).

## DISCUSSION

We have demonstrated that the prevalence of vertebral fractures in AS, in a young male population, was very high (up to 1 in 3 patients had fractures). To estimate the prevalence we used a representative sample drawn randomly from a national registry and semiquantitative methods for case

**Table 1.** Characteristics of the patients included in the study by vertebral fracture status. Associations of the different characteristics to prevalent fractures. Results are presented as mean  $\pm$  standard deviation unless otherwise specified.

Variable	Total n = 176	With Fractures, n = 57	Without Fractures, n = 119	OR (95% CI)	p
Age, yrs	48.6 $\pm$ 13.1	54.3 $\pm$ 12.8	45.9 $\pm$ 12.4	1.05 (1.03–1.08)	< 0.001
Women, n (%)	38 (21.6)	5 (8.8)	33 (27.7)	0.25 (0.09–0.68)	0.007
Disease duration, yrs	22.5 $\pm$ 12.6	26.1 $\pm$ 12.6	20.8 $\pm$ 12.3	1.03 (1.01–1.06)	0.011
Age at disease onset, yrs	26.2 $\pm$ 9.7	28.1 $\pm$ 10.8	25.2 $\pm$ 9.1	0.09 (0.93–1.00)	0.071
BASFI	3.6 $\pm$ 2.7	4.3 $\pm$ 2.9	3.2 $\pm$ 2.6	1.16 (1.03–1.30)	0.015
BASDAI	4.4 $\pm$ 2.4	4.9 $\pm$ 2.1	4.2 $\pm$ 2.4	1.13 (0.98–1.29)	0.085
ASQoL	7.1 $\pm$ 5.1	8.1 $\pm$ 5.0	6.7 $\pm$ 5.1	1.05 (0.99–1.12)	0.100
BASRI-TS	6.2 $\pm$ 3.1	7.6 $\pm$ 3.2	5.6 $\pm$ 2.8	1.25 (1.12–1.39)	0.001
BASRI-T	7.2 $\pm$ 3.7	9.0 $\pm$ 3.8	6.3 $\pm$ 3.4	1.22 (1.11–1.34)	0.001
Modified Schober test, cm	3.1 $\pm$ 1.6	2.6 $\pm$ 1.6	3.3 $\pm$ 1.6	0.74 (0.60–0.92)	0.007
Wall-occiput distance, cm	4.0 $\pm$ 5.9	7.1 $\pm$ 7.64	2.45 $\pm$ 4.18	1.15 (1.08–1.23)	< 0.001
Finger-floor distance, cm	17.8 $\pm$ 14.2	21.2 $\pm$ 14.7	16.1 $\pm$ 13.7	1.03 (1.00–1.04)	0.031
Lateral flexion, cm	17.2 $\pm$ 15.6	19.4 $\pm$ 19.6	16.2 $\pm$ 13.3	1.01 (0.99–1.3)	0.221
Thoracic expansion, cm	4.1 $\pm$ 2.0	3.5 $\pm$ 1.8	4.4 $\pm$ 2.0	0.78 (0.65–0.93)	0.007

BASFI: Bath Ankylosing Spondylitis Funtional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; BASRI: Bath Ankylosing Spondylitis Radiology Index; BASRI-TS: Total Spine.

**Table 2.** Location and severity of fracture.

Localization	Mild	Moderate	Severe	Total (%)
T5	7	3	0	10 (8.0)
T6	9	4	1	14 (11.4)
T7	12	2	0	14 (11.4)
T8	7	8	0	15 (12.3)
T9	9	6	0	15 (12.3)
T10	9	2	1	12 (10.0)
T11	4	1	1	6 (5.0)
T12	9	5	0	14 (11.4)
L1	6	1	0	7 (5.8)
L2	2	1	0	3 (2.6)
L3	1	3	0	4 (3.3)
L4	3	2	0	5 (4.0)
L5	1	2	0	3 (2.5)

definition. We found no association of fracture with disease activity, but solely with age, which is the strongest factor for vertebral fracture in any case.

The estimated prevalence of vertebral fractures in AS patients is extremely variable in the literature (0.4% to 18%). This wide variation could be due to patient selection,

differences in the definition of vertebral fracture, or the differences among centers<sup>8,9,10,13,28,29</sup>. There are no published studies about the prevalence of vertebral fracture in AS patients using a validated semiautomated quantitative morphometric method (MorphoXpress®)<sup>22</sup>. This method is more sensitive to detect mild vertebral fracture (height ratio decrease of 20%–25%) and this may be the reason for the increased prevalence in vertebral fracture in our patients compared to studies using other qualitative or semiquantitative morphometric methods<sup>7,8,9,10</sup>. Fractures of the vertebral body result in acute or chronic back pain or remain silent<sup>30</sup>. Such complications are sometimes overruled by attributing the back pain to disease activity, as long as a vertebral fracture is not considered in the differential diagnosis.

In our study, patients tended to have more than one fracture localized in the thoracic segment. This distribution of lesions could be explained because this segment of the spine is the most rigid, and by the hyperkyphosis of the upper part of the spine due to vertebral deformities apart from other causes<sup>31</sup>. We observed a significant difference in the prevalence between sexes that yielded a clear indirect association through higher BASRI scores and lower mobility in men

**Table 3.** Absolute and relative frequency of patients with one or more fractures, by number and region.

No. Fractures	Thorax Region	Lumbar Region	Thoracolumbar Region	Total (%)
1	20	5	0	25 (43.9)
2	12	0	5	17 (29.8)
3	1	0	1	2 (3.5)
4	7	0	2	9 (15.8)
5	1	0	2	3 (5.3)
6	0	0	1	1 (1.8)
Total	41	5	11	57 (100)

Table 4. Results from multivariate logistic regression analysis of variables associated with prevalent vertebral fractures in AS.

Variable	OR (95% CI)	p
Age, per year	1.05 (1.01–1.09)	0.027
Female sex	0.45 (0.13–1.52)	0.196
Disease duration, per year	0.97 (0.93–1.01)	0.172
BASFI, per score	0.97 (0.76–1.25)	0.831
BASDAI, per score	1.09 (0.84–1.41)	0.534
BASRI-TS, per score	0.73 (0.45–1.17)	0.198
BASRI-T, per score	1.43 (0.97–2.10)	0.070
Schober test, per cm	1.07 (0.75–1.53)	0.691
Wall-occiput distance	1.10 (1.00–1.21)	0.053
Finger-to-floor, per cm	1.01 (0.97–1.04)	0.726
Lateral flexion, per cm	1.01 (0.99–1.04)	0.289
Thoracic expansion, per cm	0.99 (0.77–1.28)	0.952

than in women, despite lower levels of current disease activity and lower age in the men. However, in multivariate analyses, age remained the only independent predictor of vertebral fracture.

Our study had a number of limitations, the sample size being the most important. The sample size was sufficient to estimate incidence but too small to detect associations with risk factors other than those that are well established, such as age. A larger study would probably establish whether the variables less strongly associated with fracture behave as real independent predictors.

Vertebral fracture is a frequent complication, of which there is little recognition. On suspicion of a vertebral fracture, radiographs of the spine should be performed, as suggested by Ralston, *et al*<sup>8</sup>. The high rate of vertebral fracture will justify the establishment of early diagnostic measures to assess the candidate for BMD in early stage disease and starting an early treatment in order to avoid complications arising from osteoporosis. Bone density measurement should not be performed routinely in patients with AS, but criteria should be made available in the near future. Selection of the BMD measurement technique should be based on equipment availability and on patient status. Moreover, dual-energy x-ray absorptiometry should be the method of first choice in patients with mild AS, and quantitative computed tomography in patients with more developed AS<sup>32</sup>.

On suspicion of a vertebral fracture, radiographs of the spine should be performed. Moreover, drug treatment for osteoporosis should be considered in patients with a BMD with a T score < -2.5 or with a vertebral fracture. In the absence of studies, the treatment of choice will be that used for postmenopausal osteoporosis<sup>33</sup>.

This is the first study on the prevalence of vertebral fracture in a representative sample of Spanish patients with AS (mild and long-lasting disease); and to our knowledge, this is also the first study of the prevalence of vertebral fracture using a new, validated semiautomated quantitative morphometric method, MorphoXpress<sup>22</sup>, which allows fast and reli-

able assessment of vertebral deformities. Osteoporosis and vertebral fracture are now well recognized features in AS, but their diagnosis remains challenging. Prospective studies are needed to evaluate to what degree such fractures can be prevented by therapy.

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