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# Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: A systematic review and meta-analysis

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ABSTRACT

*Objectives:* To describe the prevalence of osteoporosis, the prevalence and incidence of fractures, and the frequency of risk factors for low bone mineral density (BMD) in axial spondyloarthritis (Ax-SpA).
*Methods:* A systematic review and meta-analysis of observational studies was conducted. Medline, Embase, and Cochrane Library databases were searched with a sensitive strategy. Large cross-sectional and longitudinal studies published in the last 10 years (January 2006–2016) with representative samples of patients with Ax-SpA estimating the frequency of osteoporosis, risk factors or fractures were selected.
*Results:* After screening 3597 titles and abstracts, 46 studies were reviewed in detail, of which 35 studies had a cross-sectional design, 5 were prospective and 6 retrospective; 21 studies compared Ax-SpA patients with a control group—either healthy individuals (18 studies) or subjects with other diseases (6 studies). The prevalence of osteoporosis varied from 11.7% to 34.4% and that of fractures from 11% to 24.6%. Alcohol intake (58–61%), use of corticosteroids (11.7–66.9%), and 25-OH vitamin D deficiency (26–76%) were unexpectedly high in Ax-SpA patients.
*Conclusion:* The prevalence of osteoporosis and fractures in Ax-SpA varies between 11.7% and 34.4% and 11–24.6%, respectively. Alcohol intake, steroid use, and low levels of 25-OH-vitamin D should be taken into account in osteoporosis assessment in patients with Ax-SpA. Inconsistent results, lack of bone quality assessment, and high likelihood of bias of the published studies confirm the need for performing well-designed studies.



## Introduction

Axial spondyloarthritis (Ax-SpA) are a set of inflammatory musculoskeletal diseases affecting axial joints and frequently peripheral joints and enthesis [1]. The skeletal manifestations of Ax-SpA are mainly related to new bone formation, that is, ankylosis, periostitis, and syndesmophytes [1]. In addition, patients with Ax-SpA may develop concomitant osteoarthritis and diffuse idiopathic skeletal hyperostosis (DISH) [2,3], conditions also associated with new bone formation.

Osteoporosis (OP) is a systemic skeletal disease characterized by diminished bone mass, compromised bone strength and micro-architectural deterioration of bone tissue with increased risk for fragility fractures [4,5]. Bone mineral density (BMD), as measured by dual-energy x-ray absorptiometry (DXA), is typically used for the diagnosis of OP in men and women over the age of 50 [6], with a T-score at the hip or the spine below 2.5 standard deviations (SD) accepted as working definition [7]. These densitometric criteria are widely accepted for the diagnosis in older adults and to make decisions in conjunction with risk factors on therapeutic intervention in patients with OP.

The relation of Ax-SpA and BMD is not well understood. Abnormal calcification of spinal ligaments as well as new bone formation in the spine and peripheral joints, all hallmarks of Ax-SpA, may increase BMD as measured by DXA in spite of the presence of OP and poor bone quality. Thus, BMD may not be a sensitive marker for diagnosing osteoporosis in Ax-SpA. Inflammation-mediated bone loss, limited physical activity—directly correlated with disease activity—renal impairment that may lead to secondary hyperparathyroidism, may all potentially contribute toward a low BMD in Ax-SpA as in other rheumatic diseases. Ax-SpA patients have chronic inflammation and altered bone

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remodeling and suffer from chronic fatigue, immobility due to pain, and impaired joint movement [1]. Other risk factors for low BMD-related fragility fractures in Ax-SpA are less studied.

When designing practice protocols, a primary need is to understand how frequent a problem is. Whether osteoporosis should be included in comorbidity checklists in the care of patients with Ax-SpA should be based on the magnitude of the problem. For this reason, our group undertook a systematic review with the objective to describe (1) the prevalence of OP, (2) the prevalence and incidence of fractures, and (3) the frequency of risk factors for low BMD in patients with Ax-SpA.

## Methods

A systematic review of observational studies was conducted. Medline, Embase, and Cochrane Library databases were searched with two sensitive strategies that included synonyms of Ax-SpA, of study type, and of osteoporosis and fractures, and then with known risk factors of low BMD. Studies were selected if they included representative samples of adult patients with Ax-SpA, defined by ASAS [8] or New York criteria for ankylosing spondylitis (AS) [9], and estimated the frequency of OP or fractures, or of factors associated to low BMD. Regarding designs, large cross-sectional or longitudinal studies published in the last 10 years (January 2006–2016) were selected. The search was limited to studies in English, French, and Spanish (the full search is available as Supplementary material).

The records were downloaded to an electronic library. Duplicates, unrelated, and animals studies were deleted, and finally a clean library was uploaded in Covidence®, where two reviewers screened titles and abstracts. Any discrepancy in the decision pertaining to inclusion or exclusion of an article for full review was resolved by mutual consensus. Disagreements were resolved by a third researcher (R.C.).

We used a scale based on the one proposed by Munn for the evaluation of prevalence studies [10] to evaluate the studies quality, that included the following items: (1) Was the sample representative of the target population? (2) Were study participants recruited in an appropriate way? (3) Was the sample size adequate? (4) Were the study subjects and the setting described in detail? (5) Was the data analysis conducted with sufficient coverage of the identified sample? (6) Were objective, standard criteria used for the measurement of the condition? (7) Was the condition measured reliably? (8) Was there appropriate statistical analysis? (9) Are all important confounding factors/subgroups/differences identified and accounted for? (10) Were subpopulations identified using objective criteria?

Due to the expected variability of studies regarding the prevalence of OP or fractures, we performed random-effects meta-analysis. In a meta-analysis of prevalence, when the estimation for a study tends toward either 0% or 100%, the variance for that study moves toward zero and as a result, its weight is overestimated in the meta-analysis. Therefore, we conducted the meta-analysis with prevalence estimation that had been transformed using the double arcsine method. The final pooled result and 95% CIs were back-transformed for ease of interpretation.

We calculated point prevalence in selected studies by dividing the number of observed cases of osteoporosis, osteoporosis in femoral neck, osteoporosis in lumbar spine and fractures by the total number of observed cases of Ax-SpA. We expressed prevalence as percentage. Annual incident risk and risk of fractures in Ax-SpA patients has been also considered.

We performed random-effects meta-analysis since we expected variability in prevalence estimates from different studies. The restricted maximum-likelihood random effect model was used to derive the overall estimates and the 95% confidence intervals (CIs). In a meta-analysis of prevalence, when the estimate for a study tends toward either 0% or 100%, the variance for that study moves toward zero and as a result its weight is overestimated in the meta-analysis. Therefore, we conducted the meta-analysis with prevalence estimates that had been transformed using the double arcsine method. The final pooled result and 95% CIs were back-transformed for ease of interpretation. We studied the difference in the rate of fractures between Ax-SpA patients and healthy controls in terms of odds ratio (OR) using the Mantel–Haenszel method.

We also calculated the standardized mean diference (SMD) between BASDAI, BASRI, and CRP to discriminate between Ax-SpA patients with or without fractures.

We assessed heterogeneity through the use of both the chi-square test and the $I^2$ test statistic. We considered a $p < 0.10$ to be significant for the chi-square test due to the low power of this test and an $I^2$ of at least 50% to be significant heterogeneity. We investigated sources of heterogeneity through subgroup analysis. We assessed evidence of bias with the fail-safe N method and Egger's test. Only studies with similar risk of bias assessment were pooled in a meta-analysis and studies with high risk of bias assessment were excluded. We performed all meta-analyses using R version 3.1 and displayed results in the form of forest plots. We used the R library “metafor” to perform meta-analysis.

## Results

The databases search yielded 3944 titles (Fig. 1). After removing duplicates (347), 3597 articles were selected, of which 3464 were excluded by title and abstracts revision. Of the 133 studies retained for full-text review, 46 were finally included.

Among the studies included, 35 had cross-sectional design and 11 were longitudinal (5 prospective and 6 retrospective). Most of studies were in English. Only one study was captured in French [11]. The studies included had ethnic representation from North and South America, Europe, Africa, and Asia.

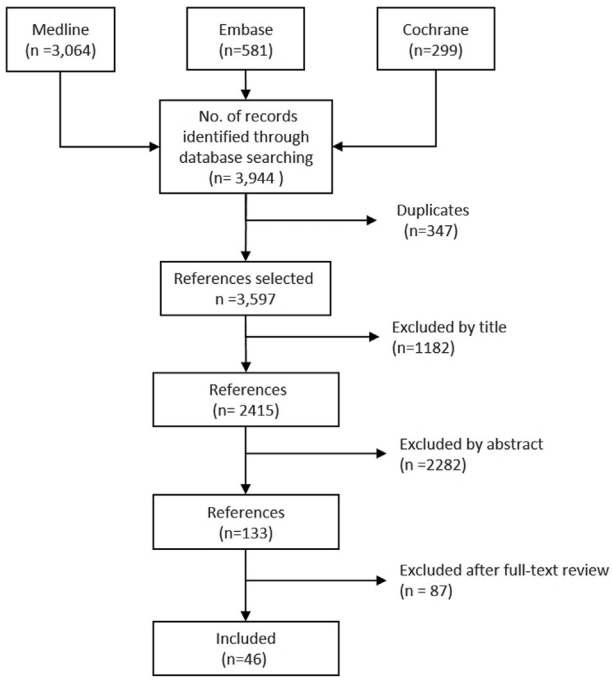


**Fig. 1.** Flow diagram of studies captured, reviewed and included.