Review

The Fascinating Paradox of Osteoporosis in Axial Spondyloarthropathy

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ABSTRACT. Low bone mineral density (BMD) is a recognized feature of axial spondyloarthropathy (axSpA). However, the osteoproliferation inherent in axSpA can make traditional dual-energy x-ray absorptiometry assessment inaccurate, particularly in structurally advanced disease. As a result, much about osteoporosis in axSpA is unknown. There is a wide variation in prevalence figures for low BMD in the literature. There is also no consensus regarding risk factors for developing low BMD in axSpA. It is accepted that there is an excess of vertebral fractures in patients with axSpA, but the role of low BMD in contributing to this risk is virtually unknown. This article provides a comprehensive review of the current knowledge regarding low BMD in axSpA. It highlights our current BMD measurement techniques along with their potential pitfalls, and discusses the significance of BMD in vertebral fractures. It also identifies gaps in our knowledge and makes recommendations for future research. (First Release October 1 2017; J Rheumatol 2017;44:1767–76; doi:10.3899/jrheum.170051)

Key Indexing Terms:
AXIAL SPONDYLOARTHROPATHY
BONE MINERAL DENSITY
OSTEOPOROSIS
DUAL-ENERGY X-RAY ABSORPTIOMETRY

Osteoporosis can be defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture"[1]. It is a recognized entity in many inflammatory diseases. In rheumatoid arthritis, it is widely accepted that low bone mineral density (BMD) is an extraarticular feature of the disease[2], with the prevalence of osteoporosis up to twice that of the general population and an increased risk of fractures. Similar data have been shown in juvenile idiopathic arthritis, where generalized loss of BMD and an excess of fractures, both vertebral and nonvertebral, are noted[3]. In psoriatic arthritis, the data are less robust, but point toward a high prevalence of low BMD[4].

BMD in Axial Spondyloarthropathy

There is growing interest in BMD in axial spondyloarthropathy (axSpA). It is now accepted that patients with axSpA have a higher prevalence of both osteopenia and osteoporosis, when compared to age- and sex-matched controls. However, the reported prevalence of low BMD varies widely, ranging from 4% to 58% (Table 1)[5–30]. There are many reasons underlying this discrepancy. First, there is a wide variation in the patient recruitment techniques used. Second, different techniques are used to evaluate BMD. A further confounder is the change in classification criteria published by the Assessment of Spondyloarthritis International Society in 2009[31]. Older studies exclusively used patients with ankylosing spondylitis (AS) as defined by the modified New York criteria, whereas newer ones use a combination of patients with axSpA and patients with AS. All these factors make it difficult to compare the existing literature accurately, thus limiting our understanding of the scale of the problem.

There are many undisputed facts. Almost all the literature agrees that patients with established axSpA have a higher prevalence of low BMD than controls (Table 1). However, this problem is not restricted to late disease. BMD begins to decline early in the disease process, with low BMD evident in 40–50% of axSpA patients with an average disease duration of only 6 years[29]. A diagnosis of axSpA is associated with low BMD, regardless of disease duration. In fact, the presence of low BMD, defined as a T score of ≤ –2 SD, has been shown to have good predictive value (positive likelihood ratio of 2.6–3.1) in diagnosing axSpA in patients with suggestive symptoms[12]. Another study also found that patients with nonradiographic (nr)-axSpA had significantly lower lumbar spine BMD than patients with mechanical lower back pain[5].

Measurement Techniques to Detect Low BMD

Currently, the gold standard for assessing BMD is posteroan-

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Accepted for publication July 11, 2017.

The Journal of Rheumatology 2017; 44:12; doi:10.3899/jrheum.170051

Table 1. Summary of studies outlining prevalence of low BMD in axial spondyloarthritis.

Author	Design	Recruitment	Study Population	N (M/F)	Disease Duration, yrs, mean	BMD Measurement Technique(s)	Result
Akgol[5]	Cross-sectional	Consecutive	LBP[$]	46 (32/14)	1.25	DEXA: AP LS, FN	LS BMD lower in nr-axSpA than mLBP patients. Low BMD associated with spinal inflammation on MRI (LS, FN).
Arends[6]	Cross-sectional	Consecutive	AS[†]	128 (93/35)	14	DEXA: AP LS, PF	57% had LS or TF BMD T score ≤ –1. Difference between LS and TF BMD positively correlated with disease duration.
Briot[7]	Cross-sectional	DESIR* cohort baseline visit	IBP[††] axSpA criteria: 71.4%	332 (174/158)	M: 1.6, F: 1.7	DEXA: LS, TF, FN	Low BMD: 11.5% LS, 4.2% hip, 13% both sites. LS BMD significantly lower in patients with BME. Lower BMD (LS, TF) in patients fulfilling ASAS criteria.
Capaci[8]	Cross-sectional	NR	AS[†]	73 (49/24)	11.8	DEXA: AP LS, TF	Mild AS: low BMD 68.4% at LS, 51.9% TF. Advanced AS: low BMD 54.3% at LS, 91.7% TF. LS BMD similar in mild and advanced AS. Frequency of osteoporosis (TF) higher in patients with advanced AS.
Devogelaer[9]	Cross-sectional	NR	AS[†]	70 (60/10)	15.4	SPA: radius DEXA: LS SE-QCT: LS	DEXA LS BMD significantly lower in patients than controls. QCT: BMD lower in patients than controls.
Donnelly[10]	Cross-sectional	Consecutive	AS[#]	87 (62/25)	M: 16.3, F: 16.6	DEXA: AP LS, FN, WB	LS BMD significantly lower in M than F. BMD reduced in LS and FN in early disease. LS BMD increased in late disease. FN BMD further decreased in late disease.
El Maghraoui[11]	Cross-sectional	Consecutive	AS[†]	43 (43/0)	6.8	QCT: LS	Mean LS BMD significantly lower in patients with AS than controls.
Forien[12]	Cross-sectional	Retrospective	axSpA[††] axSpA, n = 193 nr-axSpA, n = 61	193 (122/71)	11.2	DEXA: AP LS, FN, TF	Prevalence of low BMD: 26.4% (LS), 13.6% (TF), 40.3% (at least 1 site). Nr-axSpA: LS BMD lower than controls (T score ≤ –2 in 28.1% vs 9.7%; p = 0.01). LR+ of low BMD for axSpA diagnosis: 2.6 (LS), 3.12 (TF). LR+ of low BMD for nr-axSpA diagnosis: 2.9 (LS), 2.54 (TF).
Geusens[13]	Cross-sectional	Consecutive	SpA[‡]: 73.3% AS, 10.3% PsA, 4.6% EnA, 11.8% uSpA	390 (175/215)	10.8	DEXA: AP LS, FN, TF	T score ≥ –1: 79.7% (LS), 59.5% (FN). T score between –1 and –2.5: 17.2% (LS), 36.4% FN. T score ≤ –2.5: 3.1% (LS), 4.1% (FN).
Ghozlani[14]	Cross-sectional	Consecutive	AS[†]	80 (67/13)	10.8	DEXA: AP LS, FN, TF	Prevalence of osteoporosis at any site: 25%
Gratacos[15]	Longitudinal Mean followup 19 mos	Consecutive	AS[‡‡]	34 (27/7)	Active AS: 7.5 Inactive AS: 5.3	DEXA: AP LS, FN	Active AS had significant bone mass loss at LS (5%) and FN (3%).
Grazio[16]	Cross-sectional	Random	AS[†]	80 (46/34)	21.8	DEXA: AP LS, TF, FN	Osteopenic: 20% LS, 26.2% TF, 47.5% FN. Osteoporotic: 25% LS, 7.5% TF, 22.5% FN. Significantly more patients osteoporotic at LS than TF.
Nigil Haroon[17]	Cross-sectional	Toronto Western Hospital Spondylitis Clinic	AS[†]	53 (29/24)	17	DEXA: AP LS, FN, TF HRpQCT: distal radius and tibia	Osteopenia: 34% (M: 31%, F: 38%). Osteoporosis: 11% (M: 10%, F: 13%). vBMD lower at distal radius and tibia in AS than controls.

Table 1. Continued.

Author	Design	Recruitment	Study Population	N (M/F)	Disease Duration, yrs, mean	BMD Measurement Technique(s)	Result
Jun[18]	Cross-sectional	Consecutive	AS†	68 (68/0)	68 mo	DEXA: PA LS, TF, FN	Lower BMD in AS patients (LS, TF, FN) than controls.
Karberg[19]	Cross-sectional	Consecutive	AS†	103 (66/37)	I (≤ 5 yrs): 2.5 II (5–10 yrs): 7 III (> 10 yrs): 19.7	DEXA: AP LS, FN DEQCT: LS pQCT: radius	Prevalence (%) of osteopenia and osteoporosis at each site: DEXA LS: 31, 14 DEQCT LS: 44, 11 DEXA FN: 52, 24 pQCT radius: 16, 1. DEXA FN classified more osteoporosis than DEXA LS or DEQCT in longer disease. DEQCT classified increasing % of patients as osteoporosis with increasing disease duration; DEXA LS was the opposite.
Klingberg[20]	Cross-sectional	Randomized from larger osteoporosis study[21]	AS†	69 (69/0)	23	DEXA: AP LS, lat LS, FN, TF, radius QCT: LS HRpQCT: radius and tibia	vBMD lower in AS than controls by HRpQCT (radius/tibia). Prevalence (%) of osteopenia and osteoporosis at LS: AP DEXA: 19, 6 QCT: 30, 38
Klingberg[21]	Cross-sectional	Invited from database	AS†	204 (117/87)	24	DEXA: AP LS, lat LS, FN, TF, radius	≥ 50 yrs: osteopenia 43.6%, osteoporosis 20.8%. < 50 yrs: 4.9% low BMD. LS most common location for low BMD, followed by radius, then FN. Lat LS significantly lower than AP LS BMD.
Korkosz[22]	Longitudinal 10-yr followup	NR	AS†	15 (15/0)	16.5	DEXA: AP LS, TF, FN SE-QCT: LS	QCT baseline: n = 5 osteopenia, n = 6 osteoporosis. Significant decrease in BMD in LS by QCT over 10 yrs. DEXA LS: increased BMD. FN/TF: no significant change in BMD. No correlation between QCT and DEXA.
Lange[23]	Cross-sectional	NR	AS†	84 (53/31)	I: 9 II: 20 III: 21 IV: 32	DEXA: AP LS, TF; SE-QCT: LS	DEXA: osteopenia in 5% and osteoporosis in 9.2%. SE-QCT: osteopenia 11.8%, osteoporosis 30.3%.
Maillefert[24]	Longitudinal 2-yr followup	Consecutive	AS†	54 (35/19)	12.4	DEXA: PA LS, FN	Baseline: FN 39% osteopenic and 11% osteoporotic; LS 39% osteopenic, 17% osteoporotic. Followup: significant bone loss at FN, not at LS; no significant change in proportion of osteopenic and osteo porotic patients.
Mitra[25]	Cross-sectional	Consecutive	AS¥	66 (66/0)	9.85	DEXA: AP LS, FN	Reduced BMD (LS, FN) in AS compared to controls.
Toussirot[26]	Cross-sectional	Consecutive	AS†	71 (49/22)	10.6	DEXA: AP LS, FN	Prevalence (%) of normal BMD, osteopenia and osteoporosis at each site: LS: 53.5, 32.4, 14.1 FN: 73.2, 22.5, 4.3
Ulu[27]	Cross-sectional	Consecutive	AS†	59 (50/9)	11.5	DEXA: PA LS, lat LS, TF	PA LS: osteopenia 51%, osteoporosis 15%. FN: osteopenia 46%, osteoporosis 12%. Lat LS ≤ T score –2.5: 32%.

Table 1. Continued.

Author	Design	Recruitment	Study Population	N (M/F)	Disease Duration, yrs, mean	BMD Measurement Technique(s)	Result
Ulu[28]	Cross-sectional	Consecutive	AS†	86 (69/17)	11.74	DEXA: PA LS, lat LS, TF, FN	Comparison with control group: FN, TF and lat LS significantly lower in AS patients. No significant difference in PA LS between groups. PA LS significantly higher in late versus early AS.
Van der Weijden[29]	Cross-sectional	Consecutive	SpA¥¥ + IBP: AS 72% uSpA 12% PsA 8% IBD 4% ReA 4%	130 (86/44)	6.3	DEXA: AP LS, PF	Prevalence of low BMD: Osteopenia 28.5% (FN), 30.8% (LS), 37.7% (both) Osteoporosis 2.3% (FN), 7.7% (LS), 8.5% (both). No significant differences in BMD between hip and LS.
Venceviciene[30]	Longitudinal 48-mo followup	Consecutive	SpA¥¥: AS 51% PsA 27% EnA 10% ReA 12%	41 (34/7)	62.2 mos	DEXA: PF	27% of patients had BMD loss over the 48 mos.

Classification criteria for inclusion not reported. $ Chronic lower back pain (LBP), divided into 2 groups – 1. fulfill ASAS criteria; 2. mechanical LBP. † Fulfilling modified New York criteria. * DESIR cohort: a prospective, multicenter French cohort of patients with early IBP suggestive of SpA. †† Symptoms suggestive of axSpA according to local rheumatologist's assessment. ‡ SpA diagnosis made by treating rheumatologist. ‡‡ < 10 yrs duration, no ankylosis, persistent inflammatory disease activity. ¥ modified Schober's test ≥ 5 cm, radiographically normal hips, absent or incipient syndesmophytes. ¥¥ European Spondylarthropathy Study Group criteria. AP: anteroposterior; AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis International Society; axSpA: axial spondyloarthropathy; BMD: bone mineral density; BME: bone marrow edema; DEQCT: dual-energy quantitative computed tomography; DEXA: dual-energy x-ray absorptiometry; EnA: enteropathic arthropathy; FN: femoral neck; HRpQCT: high-resolution peripheral quantitative computed tomography; IBP: inflammatory back pain; lat LS: lateral lumbar spine; LR+: positive likelihood ratio; LS: lumbar spine; mLBP: mechanical lower back pain; MRI: magnetic resonance imaging; nr-axSpA: nonradiographic axial spondyloarthritis; NR: not reported; PA: posteroanterior; PF: proximal femur; pQCT: peripheral QCT; PsA: psoriatic arthropathy; ReA: reactive arthritis; SE-QCT: single-energy QCT; SpA: spondyloarthropathy; SPA: single-photon absorptiometry; TF: total femur; uSpA: undifferentiated SpA; vBMD: volumetric bone mineral density; WB: whole body; IBD: inflammatory bowel disease.

terior (PA) dual-energy x-ray absorptiometry (DEXA) at the spine and hip, as recommended by the International Society of Clinical Densitometry (ISCD)[32]. However, the hallmark of axSpA is sacroiliitis and spinal damage due to both bony erosion and abnormal bone formation. This can lead to the development of syndesmophytes, perivertebral bone formation, ankylosis of the zygapophyseal joints, and pathologic new bone formation in the ligamentous apparatus. In severe cases, complete fusion of the spine can occur. This extensive osteoproliferation can falsely raise the BMD when PA (conventional) DEXA is used, giving an illusion of reassuringly normal BMD, even in cases where osteoporosis may be present. A study of 73 patients with AS using PA DEXA found that the frequency of low BMD in patients with mild disease was 68.4% in the lumbar spine, but the prevalence dropped to 54.3% in advanced cases[8]. This contrasted with the hip, where the prevalence increased from 51.9% in patients with mild disease to 91.7% in advanced cases. As the disease duration increased, there was a paradoxical rise in lumbar spine BMD, but decline of total hip BMD.

The optimal method to identify BMD loss is under dispute. The literature is conflicted as to whether BMD loss in axSpA is a local or systemic process. Low BMD was significantly more common in 103 patients with AS at femoral neck than at the lumbar spine, measured by DEXA or dual-energy quantitative computed tomography (DEQCT)[19]. However, another study of 71 AS patients with a mean disease duration of 10.6 years found that the prevalence of low BMD was higher than controls at the lumbar spine, but not at the femoral neck[26]. Yet other DEXA studies have shown the central and peripheral skeletons are equally affected by low BMD[21].

In view of the limitations of traditional PA DEXA, alternative methods to assess BMD in patients with axSpA are clearly indicated. QCT has the advantage of measuring volumetric BMD (vBMD) without being affected by cortical artifacts, a technique that is highly attractive for patients with AS. In a study of 69 patients with AS, investigators found that QCT of the lumbar spine detected significantly more cases of osteoporosis and osteopenia than anteroposterior (AP) DEXA[20]. High-resolution peripheral QCT (HRpQCT), a newer technique that provides knowledge about bone microarchitecture, was also performed[20]. This demonstrated lower vBMD in the distal radius and tibia of patients with AS than in controls. It also demonstrated strong correlations between central and peripheral trabecular vBMD[20], suggesting a systemic pattern of bone loss.

Although QCT of the lumbar spine has advantages over PA DEXA, the radiation dose associated with it makes safer methods desirable. Lateral DEXA scanning of the lumbar spine exclusively examines the BMD of the trabecular component of the bodies of the vertebrae, thus excluding the cortical-rich posterior components of the spine. Because osteoproliferation predominantly affects the cortical aspect of the spine, lateral DEXA should, in theory, be less affected by the changes that occur in the spine of patients with axSpA. Similar to axSpA, the degenerative changes that occur in the spine with age can also cause overestimation of BMD when using PA DEXA[33]. Lateral DEXA has been shown to identify more patients with age-related bone loss than AP conventional DEXA, in both men and women[33]. Previously, lateral DEXA was performed with the patient lying on their side. However, precision was very low and was deemed too insensitive to have any clinical use. The modern method to acquire lateral DEXA scans is that the arm of the DEXA scan is rotated 90° and is obtained without the patient moving. Supine lateral measurements have been shown to offer similar precision to the standard AP DEXA scan[34].

In AS, lumbar spine BMD was significantly lower with lateral DEXA measurement than with AP projection and significantly more cases of osteoporosis were detected (26% vs 16%; $p < 0.001$)[21]. Therefore, lateral DEXA is a promising tool to identify cases of osteoporosis without being affected by the osteoproliferation associated with axSpA.

Trabecular bone score (TBS) is a recently emerged tool obtained by reanalyzing AP lumbar spine DEXA images and evaluating variations in grey-level texture from pixel to pixel. It can distinguish between different microarchitectures that have the same bone density. The higher the TBS, the stronger the microarchitecture of the bone, which in turn is more resistant to fracture. In the general population, TBS is related to fracture risk[35]. There is a paucity of literature on axSpA, but 1 study showed that TBS was not influenced by syndesmophytes in contrast to AP DEXA measurement of the spine, although it did not identify prevalent fractures[36]. More research is needed to determine whether TBS would be a useful tool in patients with axSpA.

Factors Associated with Low BMD

The risk factors for reduced BMD are well outlined in the general population. Unfortunately, evidence supporting patient and disease characteristics associated with bone loss in axSpA is inconsistent (Supplementary Table 1, available from the authors on request) and largely based on cross-sectional studies, where causal links are harder to establish.

Differences between the sexes. In the general population, women have a much higher risk of osteoporosis than men[37]. However, the current literature is conflicted regarding a male/female effect on BMD loss in patients with axSpA (Supplementary Table 1, available from the authors on request). Cross-sectional studies of AS patients with conventional DEXA measurements showed that male sex was associated with a lumbar or hip BMD T score of ≤ –1 SD[6] and the prevalence of low BMD in the spine was higher in men[27]. However, a 4-year longitudinal study[15] of patients with early AS demonstrated no sex effect on predicting bone loss, again as measured by conventional DEXA. A further longitudinal study of patients with axSpA, of whom 51% had

AS, also found no sex effect on bone loss, although only BMD measurements of hips were performed[30].

Perhaps this lack of effect is a bias owing to the historic underrecognition of axSpA in females and their subsequent underrepresentation in studies. As this disease is increasingly diagnosed in women, more robust studies with equal spread among men and women may answer this question more definitively. However, because the existing literature has an excess of men, it highlights that low BMD does indeed affect men with axSpA, a critically important point, because men and osteoporosis are not often thought of in the same sentence.

Disease duration. There is no consensus on the effect of disease duration on BMD, as illustrated in Supplementary Table 1 (available from the authors on request). As outlined earlier, BMD loss begins early in the disease course of both nr-axSpA and AS[5,8,29]. However, increasing disease duration is not consistently associated with worsening BMD[26,27], but this likely reflects the difficulty in assessing BMD in late disease, owing to the higher prevalence of structural damage. The difference between PA lumbar spine and hip T scores measured by DEXA increases in tandem with disease duration[6]. However, lateral DEXA measurements appear to correlate better with disease duration[28].

BASDAI. One of the most frequently used tools to assess disease activity is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a patient-reported outcome (PRO)[38]. Many DEXA studies, both cross-sectional[21] and longitudinal[15], have found no correlation between BMD and BASDAI. There are a few notable exceptions, however. One cross-sectional study measured BMD of the lumbar spine with QCT[39] and found a higher mean BASDAI in patients with osteoporosis of the spine than without (8 vs 4; $p < 0.05$). Conversely, Arends, *et al*[6] found that when patients with AS were categorized as low BMD if the T score of the lumbar spine or hip was ≤ –1 SD by DEXA, then a lower BASDAI was independently associated with low BMD (hip or spine).

A disadvantage of BASDAI is that it reflects the current disease activity and does not detect periods of potentially prolonged active disease in the past. Therefore, it is possible that a once-off calculation of BASDAI cannot predict BMD loss, but that the average score over time would be more useful. This hypothesis is supported by a 4-year longitudinal DEXA study of patients with SpA[30], in which the patient group with more BMD loss had a higher average BASDAI score than those without BMD loss.

BASMI. The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a validated tool to objectively assess spinal mobility[40]. Several cross-sectional studies have found an association between higher total BASMI and low BMD (Supplementary Table 1, available from the authors on request). A longitudinal study[30] demonstrated that over 4 years, a deterioration in lateral flexion and intermalleolar distance readings of patients with SpA was associated with BMD loss at the hips (lumbar spine not assessed).

Inflammatory markers. Many studies (Supplementary Table 1), both longitudinal and cross-sectional, including DEXA and QCT, have found an association between higher C-reactive protein or erythrocyte sedimentation rate and lower BMD. However, to date, whether the addition of laboratory variables to PRO, in scores such as the Ankylosing Spondylitis Disease Activity Score, improves the predictive value of low BMD has not been investigated.

Radiological severity. From the Outcome Assessments in AS International Study cohort[41], we know that more active disease is associated with progressive radiographic spinal change, as measured by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) or the Bath AS Radiological Index (BASRI). The effect of radiographic damage on BMD is less clear (Supplementary Table 1, available from the authors on request). In the presence of syndesmophytes, more patients with AS had low BMD when measured by DEXA of femoral neck or DEQCT of lumbar spine than when AP DEXA of the spine was used[19]. After 10 years of disease duration, AP DEXA of the lumbar spine did not detect any cases of osteoporosis, and DEQCT at lumbar spine and DEXA of femoral neck were used instead. Another study using QCT to assess BMD of the lumbar spine showed that increasing mSASSS correlated significantly with a lower volumetric BMD in the lumbar spine[20]. In that study, peripheral bone microarchitecture, as measured by HRpQCT of the radius and tibia, was also worse in patients with more advanced structural damage, a finding supported by Nigil Haroon, *et al*[17].

Vertebral Fractures

The clinical significance of osteoporosis is in the increased risk of fractures. In the general population, this risk is extremely well outlined[37]. It is less well defined in axSpA.

Multiple studies have shown that AS involves an increased risk of vertebral fractures (VF) compared to age- and sex-matched controls (Table 2[42,43,44,45,46,47]). It is also known that VF in patients with AS have a higher rate of complications, including devastating neurological outcomes[48], than the general population. However, studies have demonstrated a wide variation in prevalence, anything up to 32% (Table 2). A large primary care–based case-control study in the United Kingdom[47] selected 231,436 cases of fracture, vertebral and nonvertebral, recorded in the General Practice Research Database and matched with 231,362 controls. Patients with AS had an increased risk of clinical VF than controls, even when corrected for potential confounders (OR 3.26, 95% CI 1.51–7.02). However, the risk of peripheral fractures in patients with AS was not increased, except in a subset that had a concomitant diagnosis of inflammatory bowel disease (OR 2.79, 95% CI 1.10–7.08). A Swedish-based registry prospective study[46] identified all patients with a primary

Table 2. Studies outlining prevalence of vertebral fractures in axial spondyloarthritis.

Author	Design	N (M/F)	Study Population	Disease Duration, yrs, mean	Definition of VF	Prevalence of VF (%)	Association with Low BMD
Arends[6]	Cross-sectional	128 (93/35)	AS†	14	Radiographic[A]	20%	No association
Capaci[8]	Cross-sectional	73 (49/24)	AS†	11.8	Radiographic[B]	5.5%	No association
Donnelly[10]	Cross-sectional	87 (62/25)	AS#	M: 16.3, F: 16.6	Radiographic[B]	10.3, n = 9	No reduction in BMD by DEXA of LS, FN, and WB.
Geusens[13]	Cross-sectional	390 (175/215)	SpA‡: 73.3% AS 10.3% PsA 4.6% EnA 11.8% uSpA	10.8	Radiographic[A]	11.8%	Significantly associated with FN BMD: OR 1.38 per 1 SD decrease of T score (95% CI 1.08–1.62)
Ghozlani[14]	Cross-sectional	80 (67/13)	AS†	10.8	Radiographic[A]	18.8%	Associated with reduced BMD and T score at hip site and presence of osteoporosis at any site
Jun[18]	Cross-sectional	68 (68/0)	AS†	68 mo	Radiographic[A]	16.2%	Lower BMD at hip
Klingberg[44]	Cross-sectional	204 (117/87)	AS†	24	Radiographic[A]	11.8%	Patients with VF had significantly lower BMD at all sites compared to patients without a VF
Klingberg[20]	Cross-sectional	69 (69/0)	AS†	23	Radiographic[A]	12%	DEXA: AP and lateral lumbar BMD, lumbar vBMD and BMD of FN, and TH all lower in patients with VF. No difference in forearm DEXA. QCT: lower cortical lumbar vBMD in presence of VF.
Lange[39]	Cross-sectional	58 (38/20)	AS†	17.6	Radiographic[C]	12.1%	All VF had osteoporosis by QCT LS
Maillefert[24]	Longitudinal 2-yr followup	54 (35/19)	AS†	12.4	Radiographic[A]	3.7%	NR
Mitra[25]	Cross-sectional	66 (66/0)	AS¥	9.85	Radiographic[B]	16.7% vs 2.6% of controls (OR 5.92)	No correlation between BMD of LS or FN and VF
Montala[45]	Cross-sectional	176 (138/38)	AS†	22.5	Radiographic[A]	32.4%	NR
Robinson[46]	Prospective	17764 (M/F NR)	AS††	NR	Clinical[D]	4.1%, n = 724 Increased proportion of VF in admitted patients from 0.82% in 1987 to 11.3% in 2008	NR
Toussirot[26]	Cross-sectional	71 (49/22)	AS†	10.6	Radiographic[A]	1.4%	NR
Ulu[27]	Cross-sectional	59 (50/9)	AS†	11.5	Radiographic[E]	30.6%	VF associated with osteoporosis by lat LS DEXA
Vosse[47]	Case-control	758 (442/316)	AS†	NR	Clinical[G]	4.5%	NR

† Fulfilling modified New York criteria. # Classification criteria for inclusion not reported. ‡ SpA diagnosis made by treating rheumatologist. ¥ Modified Schober's test ≥ 5 cm, radiographically normal hips, absent or incipient syndesmophytes. †† ICD code of AS in Swedish National Hospital Discharge Registry. A: morphometric VF on radiographs, Genant[42] classification; AS: ankylosing spondylitis; B: morphometric VF on radiographs, McCloskey[43] classification; BMD: bone mineral density; C: morphometric VF on radiographs, vertebral height (thoracic/lumbar spine) height decrease > 15%; D: discharge diagnosis; E: morphometric VF on radiographs, vertebral height (thoracic/lumbar spine) height decrease > 20%; DEXA: dual-energy x-ray absorptiometry; EnA: enteropathic arthropathy; FN: femoral neck; G: VF diagnosis in General Practice Research Database, computerized records of sample of general practitioners in the United Kingdom; LS: lumbar spine; lat LS: lateral LS; NR: not reported; PsA: psoriatic arthropathy; QCT: quantitative computed tomography; SpA: spondyloarthropathy; TH: total hip; TS: thoracic spine; uSpA: undifferentiated SpA; vBMD: volumetric BMD; VF: vertebral fracture; WB: whole body; AP: anteroposterior.

discharge diagnosis of VF and concomitant diagnosis of AS admitted between 1987 and 2008 and demonstrated a prevalence of 4.1% for clinical VF among patients with AS, with the proportion of fractures increasing throughout the 22 years of the study. However, registry-based data may underestimate the true prevalence of VF because VF do not always come to clinical attention, and prevalence on radiographic studies is much higher (Table 2).

The reason for the excess risk of VF in this population has not yet been fully elucidated (Supplementary Table 2, available from the authors on request). Cross-sectional studies demonstrated that radiographic detection of VF was correlated with radiological severity of AS, by mSASSS (OR 1.17, 95% CI 1.05–1.3)[14] and BASRI (OR 1.25, 95% CI 1.12–1.39)[45]. BMD may also play a role in the excess risk of VF in patients with AS, as demonstrated by significant correlations between radiographic VF and BMD at all sites measured by DEXA (femoral neck, total hip, lateral lumbar BMD, radius and AP lumbar BMD)[44]. However, in another study, only hip and lateral lumbar spine BMD were significantly lower in the radiographic VF group than in those without fractures[28], with no correlation with AP lumbar spine BMD measurement. Yet other studies have shown no correlation between VF and BMD[10]. A study of 390 patients with axSpA found an increased risk of radiographic VF with lower femoral neck T scores[13].

Low BMD is unlikely to fully explain the excess risk of VF, and decreased bone strength may play a role. HRpQCT of the distal radius and tibia demonstrated that patients with AS had worse microarchitecture (lower cortical and total vBMD, reduced cortical thickness, increased cortical porosity) than patients without AS, despite there being no difference in BMD by DEXA between groups at either the radius or lumbar spine[17]. In another study, male AS patients with VF demonstrated significantly worse peripheral bone microarchitecture (as measured by HRpQCT of the distal radius and ulna) than AS patients without a VF[20].

Although the cause of VF is likely multifactorial, until our assessment techniques for detecting low BMD in AS are improved and standardized, it will be difficult to determine exactly what role BMD plays in the excess risk of VF that exists in this population.

EULAR Guidelines

In 2015, the European League Against Rheumatism (EULAR) published guidelines regarding imaging in axSpA[49] that acknowledged the influence of radiographic change on evaluating BMD. This led to the recommendation that hip and AP DEXA be used in patients without syndesmophytes on conventional radiography. In patients with syndesmophytes, hip DEXA should be used, supplemented by either lateral DEXA or QCT. They also recommended further research to determine which form of imaging provides the best clinical usefulness for the diagnosis and monitoring of low BMD in patients with axSpA.

These guidelines highlight the issue of low BMD in patients with axSpA, a critically important step considering that only 31.6% of rheumatologists indicated that assessing for osteoporosis was part of their routine management of patients with AS[50]. However, the guidelines are limited by the lack of evidence available. BMD loss tends to be a progressive process, particularly if untreated, and thus requires serial monitoring. ISCD guidelines state that the same machine should be used to monitor patients for BMD loss to allow for accurate comparisons[32]. However, inherent to axSpA is the progression of structural damage[41]. Therefore, if EULAR guidelines are strictly followed, AP DEXA will be used in early disease, whereas lateral DEXA or QCT will be used in later disease, which will not allow accurate comparison of BMD. Clearly, having a guideline that recommends one method of BMD assessment in the early stages of the disease and a different one in the later, more structurally advanced stages is less than ideal.

The inherent paradox of osteoproliferation and osteoporosis in axSpA hinders clinicians in accurately managing the bone loss that occurs in this population. It is largely undisputed that low BMD occurs in axSpA, but much more work needs to be done. The most pressing problem is the lack of a standardized and accurate method to detect low BMD in this population. This needs to be clarified, then validated in axSpA, to prevent both under- and overdiagnosis of osteoporosis in axSpA. Without this method, it will remain difficult to accurately define the extent of the problem, as well as to determine predictive factors, consequences, and the effect of treatment on BMD in axSpA.

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