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# **Bone mass in axial spondyloarthritis: A literature review**

Kilic E *et al*. Bone mass in axSpA

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**Abstract**

**AIM:** To review the published literature reporting bone loss in patients with axial spondyloarthritis (SpA) particularly those studies using dual X-ray absorptiometry (DXA) methods.

**METHODS:** This literature review examines the reported bone mass in patients with ax-SpA, particularly those using the DXA methods. The MedLine, Web of Science and Scopus databases were searched for relevant articles published between September 1992 and November 2013. Some of used search terms were ankylosing spondylitis (AS), SpA, spondyloarthropathy, bone loss, bone mass, osteopenia, bone mineral density, osteoporosis, densitometry. Studies in which bone loss was investigated by using DXA in patients with SpA were eligible. Each article was reviewed and the key elements were noted.

**RESULTS:** There were 286 hits on MedLine, 200 on Web of Science and 476 on Scopus. After applying inclusion and exclusion criteria, we identified 55 articles in our systematic search. The sample size of the studies varied from 14 to 332 patients with SpA. The reported age range varied from 25 to 56 years in the reviewed studies. The symptom duration of patients with axSpA varied from 1.6 to 49 years. There were more males than females in these studies. Most of the recruited females were premenopausal women. Reported HLA-B27 positivity changed between 19% to 95%. The prevalence of osteoporosis and osteopenia in patients with SpA varied from 3%-47% to 5%-88%, respectively, in the included studies. In particular, the prevalence of osteoporosis and osteopenia ranged from 2.0%-47.0% and 5.0%-78.3%, respectively, in patients with AS. There are conflicting results regarding the relationship among disease activity, acute phase response and bone mass. Some studies suggest good correlation of bone mass with disease activity and acute phase reactants.

**CONCLUSION:** Bone loss may be determined in patients with axSpA at the lumbar spine or proximal femur even in the early phase of the disease and may be associated with inflammation (bone marrow edema) at the vertebral colon.

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**Key words:** Bone mineral density; Dual X-ray absorptiometry; Osteoporosis; Spondyloarthritis; Ankylosing spondylitis

**Core tip:** Osteoporosis is a well-known problem in patients with ankylosing spondylitis and other forms of spondyloarthritis. It may begin even in the early stages of the disease and inevitably causes vertebral fractures. Bone loss can be prevented with tumor necrosis factor blocking therapy by reducing inflammation at skeletal sites. Dual X-ray absorptiometry (DXA) is the preferred method to assess bone mass in the early stages of the disease or in patients without aberrant ossification of the spine. In advanced cases DXA measurements with lateral spinal projections or quantitative computed tomography may be referred.

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**INTRODUCTION**

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by predominant involvement of the spine and/or sacroiliac joints. It consists of ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated type[1]. Axial (SpA) comprises a heterogeneous group of diseases which predominantly involve the axial skeleton and have many overlapping clinical features. The axial SpA spectrum ranges from non-radiographic axial SpA (nr-axSpA) at one end to AS at the other. Non-radiographic axial SpA (nr-axSpA) comprises SpA patients without definite sacroiliitis on pelvic X-ray[2]. The most important clinical and laboratory features of this group are inflammatory back pain, enthesitis, dactylitis, extra-articular manifestations (acute anterior uveitis, psoriasis and inflammatory bowel disease) and association with HLA-B27.

Low bone mass (osteopenia or osteoporosis) and osteoporotic vertebral fractures are well known complications of SpA, especially in AS[3]. The pathogenesis and onset of osteoporosis in SpA is not clear. The prevalence of low BMD has been reported to be as high as 47% at the hip and lumbar spine even in patients with early SpA[4]. Patients with SpA may have increased risk of bone loss as a result of high disease activity, pro-inflammatory cytokines, mechanical factors (*i.e.*, rigidity of the spine, vertebral deformities) and decrease in physical activity or mineralization defects due to subclinical gut involvement[5, 6].

Several techniques have been used to measure bone mineral density in SpA including quantitative ultrasound (QUS), quantitative computed tomography (QCT), high-resolution peripheral quantitative computed tomography (HRpQCT), single-photon absorptiometry, dual photon absorptiometry, dual-energy X-ray absorptiometry (DXA), and morphometric X-ray absorptiometry[7-11]. Among these techniques DXA can be considered as an accurate, repeatable and quantitative method to assess bone mineral density (BMD) at the spine and hip[12]. Several studies have indicated that DXA may be a misleading method to assess BMD in advanced AS. New bone formation and aberrant hyperostosis inevitably cause a pseudo increase in bone density. However the most appropriate and valid method to assess BMD in patients with advanced AS is still unclear. A systematic evaluation of DXA methods used to assess BMD in SpA is strongly needed. Therefore this comprehensive review will examine the published literature assessing bone density in patients with axial SpA particularly those studies using DXA as the measurement method.

**MATERIALS AND METHODS**

The MedLine, Web of Science and Scopus databases were searched for relevant articles published between September 1992 and November 2013. The following search terms (synonyms and combinations) were used: “ankylosing spondylitis” OR “spondyloarthritis” OR “spondyloarthropathy” AND “bone loss” OR “bone mass” OR “osteopenia” OR “bmd” OR “bone mineral density” OR “osteoporosis” OR “fracture” AND “mri” OR “ct” OR “resonance” OR “computed tomography” OR “densitometry” OR “dxa” OR “dexa”. The references of the reviewed articles were manually scanned for other relevant studies. Studies in which bone loss was investigated by using DXA in patients with SpA were eligible. The selection criteria consisted of original articles involving humans and published in English. Articles were excluded if they were case reports, review articles or meta-analyses and did not measure bone density by using DXA. Each article was reviewed and the key elements are summarized in Tables 1-3.

**RESULTS**

Figure 1 shows the flow chart and the selection process. There were 286 hits on MedLine, 200 on Web of Science and 476 on Scopus. Using the above-mentioned inclusion and exclusion criteria, we identified 55 articles (Cross sectional studies: 41, follow-up studies: 6 and interventional studies: 8) in our systematic search.

***Population of the studies***

Fifty five articles are summarized in Table 1. The sample size of the studies varied from 14 to 332 patients with SpA including AS, ReA, PsA, undifferentiated SpA and nr-axSpA. The reported age range varied from 25 to 56 years in the reviewed studies. The reported symptom duration of patients with axSpA ranged between 1.6 to 49 years. As expected, there were more males than females in these studies. Most of the recruited females were premenopausal women. Reported HLA-B27 positivity changed between 19% to 95% and vertebral fractures (VF) were reported with a prevalence of up to 39% in the reviewed studies. The prevalence of osteoporosis and osteopenia in patients with SpA varied from 3%-47% to 5%-88%, respectively, in the included studies. In particular, the prevalence of osteoporosis and osteopenia ranged from 2.0%-47.0% and 5.0%-78.3%, respectively, in patients with AS.

***Techniques used to detect BMD***

We included studies which used DXA as the technique of BMD assessment in patients with axSpA. Eleven of the 55 studies were comparative studies in which DXA techniques were compared with quantitative ultrasound (QUS)[7, 13, 14], single energy quantitative computed tomography (SE-QCT)[8], quantitative computed tomography (QCT)[9,15-19], dual-energy quantitative computed tomography (DEQCT)[20], peripheral quantitative computed tomography (pQCT)[20] and high-resolution peripheral quantitative computed tomography (HRpQCT)[9].

Regarding the comparative studies, one study demonstrated that QUS correlated with DXA[13] but this result was not confirmed in any other study[7]. On the other hand, Jansen *et al*[14] demonstrated similar performance with QUS compared to DXA in detecting osteoporosis-associated fracture risk.

Numerous QCT studies demonstrated higher prevalence of OP compared to those studies which used DXA as the assessment tool[8,9,18], whereas only one study revealed no difference between QCT and DXA[20]. Two studies revealed a good correlation between QCT and DXA[9,15], however lumbar spine DXA was shown to be less useful than QCT to detect the degree of osteopenia in late stage AS[15,17].

The change in bone formation and resorption markers including bone alkaline phosphatase (bALP), osteocalcin (OC), C-terminal cross-linking telopeptide of type I collagen (CTX), and deoxypyridinoline (DPD) is presented in Table 4. There are conflicting results regarding the levels of bone formation and resorption markers in patients with AS and other forms of SpA.

***Relationship between BMD, disease activity and acute phase reactants***

There are conflicting results regarding the relationship between disease activity, acute phase response markers and bone mass. Some studies suggested a good correlation between bone mass with disease activity[16,21-26] and acute phase reactants[4,16,21,23-28], whereas others[7,13,20,29] did not report a significant relationship.

A recent study revealed the close association between bone mineral density and MR defined acute inflammatory changes in the lumbar spine[30]. The results of this study, as well as the results obtained in patients with early inflammatory back pain, clearly defined the inflammation induced bone loss in patients with axial SpA[21,30].

***Changes in bone mass and longitudinal studies***

Patients with active disease (BASDAI>4) had significantly lower proximal femur BMD compared to patients with inactive disease, whereas spinal BMD was similar in the study by Kaya *et al*[31] After 24-mo of follow-up lumbar spinal BMD increased in both groups; however hip BMD decreased in the inactive group[31]. On the other hand, Gratacos *et al*[6] reported that BMD at the lumbar spine and at the femoral neck decreased in patients with active disease but no change was observed in patients with inactive disease after 19 mo of follow-up. There are conflicting results in follow-up studies. For examples, Maillefert *et al*[32] reported unchanged lumbar BMD but decreased femoral neck after 12 mo of follow-up, whereas Haugeberg *et al*[33] failed to demonstrate significant reduction in hip, spine or hand BMD.

CRP levels have been suggested as an independent predictor of BMD change in patients with AS[6]. Additionally, femoral neck BMD has been found to be associated with persistent systemic inflammation which was defined by elevated ESR[32]. On the other hand, another study failed to show significant interactions among spinal or hip BMD measurements and age, body mass index, disease duration, lumbar Schober, BASDAI, ESR or CRP[31] although BASFI had a significant negative effect on hip BMD[31]. An 8 year follow-up study revealed that hip bone loss was associated with raised baseline CRP levels, MR defined bone marrow edema of the SIJs and the presence of radiographic sacroiliitis[33].

***Change in Bone Mass after anti-TNF Therapy***

In all interventional studies BMD at the lumbar spine[34-41] increased in patients treated with anti-TNF therapy. Additionally, hip BMD also increased[34-37,39-41] except for one study in which hip BMD remained unchanged[38].

Baseline bALP, OC and CTX levels significantly correlated with the increase in spinal BMD at weeks 24 and 102 after anti-TNF therapy[40]. Changes in acute phase reactants as well as disease activity scores have been demonstrated to correlate with the changes in BMD measurements[36,39,41]. Spinal BMD changes were shown to be associated with changes in ESR and newly formed syndesmophytes under anti-TNF therapy[36].

**DISCUSSION**

Osteoporosis is a well-known problem in patients with AS which begins in the early stages of the disease and inevitably causes vertebral fractures[42-44]. The reported prevalence of osteoporosis in AS varies from 3% to 47% according to the measurement techniques and patient selection criteria used. Osteopenia has been reported in up to 88% of patients with SpA. An increased prevalence of spinal bone loss may occur even in early and mild forms of SpA[8,42-46].

Systemic inflammation may play a critical role in the pathogenesis of OP in patients with systemic inflammatory disorders including SpA. This notion is supported with data from studies revealing reduced spinal BMD in patients with early or mild disease without advanced structural damage at the spine[20,21,30,43,47]. In advanced cases, spinal ossifications may mislead normal or artificially increased BMD at the lumbar spine. In such cases DXA measurements of the spine with lateral projections have been suggested to improve sensitivity[27,48]. On the other hand, the precision of DXA measurements on the lateral spine is reasonably lower than on the AP spine or proximal femur[27,48].

As an alternative method QCT, which selectively measures trabecular and cortical bone density, can be used to determine spinal BMD in cases with advanced structural changes[8,9,19,20].

Dual-energy X-ray absorptiometry is known as the reference method to measure BMD. It is an accurate, reproducible, and non-invasive method with good short or long-term precision. Multiple skeletal sites can be safely and precisely assessed by DXA[49]. Direct radiography is still a valid method for assessing structural damage in patients with axial SpA; however it gives little information about bone density since demineralization needs to reach 50% in order to confirm a reliable bone loss on radiographs. Higher incidence of bone loss at the hip compared to the lumbar spine has been suggested in various studies conducted in patients with AS[7,14,15,20,24,44,46-48,50].

There are inconclusive results regarding the association between DXA measurements with clinical and laboratory findings. Bone mineral density at the lumbar spine and hip has been shown to correlate with BASDAI[16,24-26], ESR[16,24-26,28] and CRP[16,24-26,28]. However conflicting results have also been reported[7,13,20,29].

The follow-up studies included in this review revealed that BMD measurements at the proximal hip usually decreased but lumbar spinal measurements increased or were unchanged after a reasonable follow-up.

Regarding the interventional studies, we identified 8 studies which assessed the influence of TNF blocking therapy on BMD in patients with SpA. In 7 out of 8 studies, BMD at the lumbar spine and proximal hip increased after treatment with anti-TNF drugs[34-37,39-41]. The positive effects of these potent anti-inflammatory treatments (TNF blockers) on BMD indirectly support the role of systemic or local inflammation in bone metabolism.

In patients with SpA, bone loss starts in the early stages of the disease and can be prevented with TNF blocking treatments that have been shown to reduce inflammation at the skeletal sites. DXA is the most suitable technique to determine bone mass at both the lumbar spine and proximal femur in early or non-advanced cases. However it may cause misleading results particularly at the AP lumbar spine due to the aberrant ossification or degenerative changes. Despite its limitations, DXA measurements with lateral spinal projections or QCT may be a solution to this problem in patients with advanced disease.

**COMMENTS**

***Background***

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by predominant involvement of the spine and/or sacroiliac joints. Low bone mass (osteopenia or osteoporosis) and osteoporotic vertebral fractures are well known complications of SpA, especially in ankylosing spondylitis (AS). The pathogenesis and onset of osteoporosis in SpA is not clear.

***Research frontiers***

Low bone mass and osteoporotic vertebral fractures are common complications of SpA, especially in AS. The prevalence of low BMD has been reported to be as high as 47% at the hip and lumbar spine even in patients with early SpA. Patients with SpA may have increased risk of bone loss as a result of high disease activity, pro-inflammatory cytokines and decrease in physical activity or mineralization defects due to subclinical gut involvement.

***Innovations and breakthroughs***

This review includes studies, which used dual X-ray absorptiometry (DXA) as the technique of BMD assessment in patients with axSpA. In twenty percent of studies, DXA techniques were compared with quantitative ultrasound or different type of quantitative computed tomography. Among these techniques DXA can be considered as an accurate, repeatable and quantitative method to assess BMD at the spine and hip but new bone formation and aberrant hyperostosis inevitably cause a pseudo increase in bone density.

***Applications***

The most appropriate and valid method to assess BMD in patients with advanced AS is still unclear. A systematic evaluation of DXA or alternative methods used to assess BMD in SpA is strongly needed.

***Peer review***

Overall the paper is well written and the subject is certainly of interest.

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**P-Reviewer:** Daoussis D **S-Editor:** Song XX **L-Editor:** **E-Editor:**

**Table 1 Summary of the cross sectional studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Sample size**  **(M/F)** | **Mean age (yr)** | **Menopausal status pre:post** | **Disease duration (yr)** | **DXA machine** | **Dexa site (Coefficient variation %, if available)** | **Outcome** | **Conclusion** |
| Devogelaer *et al*[19] | AS:70(60/10) | 39 | 10:0 | 15.4 | Novo | SPA: non dominant radius  DXA: L2-4  QCT: 10 patients LS | DXA values at LS was decreased in the male  VF:2.9% | In patients with severe AS, DXA demonstrates normal values due to new bone formation |
| Donnelly *et al*[42] | SpA:87(62/25)  AS:82.5%  PsA:8% | M:43.5  F:44.8 | NM | M:16.3  F:16.6 | Hologic | L1-4(0.7), FN(1.5), whole body | AS: in early disease LS-BMD decreased, in advanced AS increased  Lumbar Spine density lower in M than F  VF 10.3% | DXA is doubtful to truly reflect the state of demineralization in the spine and more emphasis should be placed on measures on FN-BMD |
| Mullaji *et al*[43] | AS:33(27/6)  -Mild:22(16/6)  -Adv:11(11/0) | 32.3 | 0:6 | M  -Mild:8.7  -Adv:11.7  F  -Mild:6.8 | Norland | Whole body | LS BMD lower in mild and higher in advanced AS than C  In Adv. AS, LS BMD higher than mild AS and C  HLA-B27: 100%  LS, FN and leg BMD decreased in mild AS compared with C in men | The relation between BMD and severity of disease in the axial skeleton may help to explain the etiology and pathogenesis of the spinal deformities and complications of this disabling condition |
| Singh *et al*[44] | AS:14(14/0) | 50 | NA | NM | Hologic | AP L1-4, non dominant hip | FT BMD lower than LS  Osteopenia at FN:64%, LS:36% | Femoral measurements of BMD are superior to lumbar measurements in the detection of osteopenia in patients with AS |
| Acebes *et al*[51] | AS: 18(16/2) | 44.7 | NM | 10.3 | Hologic | L2-4, FN | M: OP 0% osteopenia:53.8%  F: OP and Osteopenia 0%  HLA-B27:100% | Osteopenia in AS occurs as a result of high resorption of bone with normal formation |
| Meirelles *et al*[50] | AS:30(27/3) | 37 | 3:0 | 17 | Hologic | L1-4, PF | LS openia:23% OP:27%  FT: openia:55% OP:31%  AS has lower BMD at LS and proximal femur than C | Bone mass loss in AS is better evaluated in the proximal femur, because of almost free of artifacts |
| Juanola *et al*[52] | AS:18(0/18) | 36.7 | 18:0 | 15.1 | Hologic | L2-4(0.5), FN(1) | HLA-B27: 94.4%  OP: 5.6%, Osteopenia: 11.1%  VF: 5.6% | Slight reduction in BMD in premenopausal women with early AS, but the difference was not statistically significant |
| Mitra *et al*[3] | AS:66(66/0) | 37.8 | NA | 9.9 | Hologic | L1-4(1.4), FN(2.9) | In patients with AS, BMD and T scores were reduced in both LS and FN  VF:16.7% in AS, 2.6% in C | AS patients with mild disease had higher risk of VF compared with the normal population and this increased with the duration of disease |
| Borman *et al*[53] | AS:32(32/0) | 39.1 | NA | 14.8 | Hologic | Lat L1-4(2.7) | L1-4 T score and BMD similar among AS and C  BMD was similar among active and inactive AS.  VF:31.2%  Osteopenia:34.3% in AS, 21.8%in C  OP: 34.3% in AS, 6.2%in C | The incidence of osteoporosis is high in AS and patients with active disease are have risk for developing osteoporosis |
| Dos Santos *et al*[54] | AS:39(39/0) | 37.6 | NA | 8.4 | Hologic | Whole body | HLA-B27 79.5%  AS had bone loss at spine compared with control group.  46% of patients with AS had Z score < –1.5 SD. | AS is associated with bone loss, mainly concerning the lumbar spine, in patients whose disease is biologically most active |
| Toussirot *et al*[13] | AS:71(49/22) | 39.1 | 22:0 | 10.6 | Lunar | L2-4(1), left FN(1.5) | HLA-B27: 84.5  AS: Lumbar osteopenia:32.4%, OP:14.1% higher than C  Femur: osteopenia:22.5%, OP:14.1% higher than C  Good correlation between lumbar, femur, total BMD with QUS | AS has decreased lumbar, hip and total body BMD but soft tissue composition was not involved in disease process |
| Grisar *et al*[55] | AS:30(22/8)  PsA:23(17/6)  ReA:10(5/5) | AS:44.2  PsA:45.2  ReA:47.8 | NM | AS :9.2  PsA :10.4  ReA :1.3 | Hologic | LS and non dominant hip | AS; OP 47% |  |
| Speden *et al*[7] | AS:66(0/66) | 43.4 | 50:16 | 21.1 | Hologic | PA L1-4(1), non-dominant hip(1.8) and Whole body(0.82) | Hip and whole body BMD reduced in AS  Femoral neck OP:6%, osteopenia:52% in AS and higher than control  Lumbar OP:8%, osteopenia:18% in AS | Women with AS have lower hip BMD without correlation with disease duration suggesting that low BMD is an early feature of disease |
| Capaci *et al*[56] | AS:73(49/24) | 37.3 | NM | 11.8 | Hologic | L1-4, FT | L BMD similar in mild and advanced AS, F BMD lower in advanced AS  In advanced AS osteopenia or OP higher in the total hip than mild AS  VF:5.5%  LS Osteopenia or OP :68.4%-54.3  PF osteopenia or OP: 51.9-91.7 (mild-advanced) | Syndesmophytes and ligament calcification may mask bone loss in LS therefore hip BMD more convenient to asses OP in AS |
| Jansen *et al*[14] | AS:50(35/15) | 52 | NM | 21 | Hologic or Lunar | AP LS, FN | HLA-B27 88%  VF LS:6%  LS openia:54% OP:15%  FN openia:72% OP:20% and 70% of them correctly diagnosed with QUS. | The performance of QUS is similar to DEXA in finding patients with osteoporosis-associated fractures  Both osteoporosis and fractures are common sequel in AS |
| Obermayer-Pietsch *et al*[16] | AS:104(71/33) | 41 | 33:0 | 15 | Hologic or Lunar | LS(2.2-0.9), PF(2-1.6)  QCT(1) | HLA-B27:19-93%  OP:25%  In male AS patients FokI genotypes were independent predictors of low BMD. | Vitamin D receptor gene may be involved in BMD differences, bone metabolism and inflammatory processes in ankylosing spondylitis |
| Baek *et al*[47] | AS:76(76/0)  mild AS:59.2%  severe AS:40.8% | 28.1 | NA | 9.4 | Lunar | L2-4, PF | BMD and T score at FN and FT lower in severe AS than mild AS but not at LS.  Osteopenia: 48% in mild AS (more frequently at LS than proximal Femur) and 31% in severe AS. | Osteopenia is frequently observed in both severe and mild AS with little mobility limitation  Both BMD in severe disease are lower than in mild disease at the FT but not in the lumbar spine, probably due in part to progressing paravertebral calcification during the course of AS |
| Gilgil *et al*[48] | AS:20(20/0) | 25-63 | NA | 16.7 | Norland | PA L2-4(1),  lat L3(2.7),  left FN(1.2) | PA L2-4 BMD similar between groups but lateral L3 and FN BMD reduced in AS  No VF  Syndesmpphytes:60%  PA LS OP:20% in AS, 15% in C | Lateral L3 DXA is superior to PA DXA in detecting a decrease in BMD in patients with AS |
| Karberg *et al*[20] | AS:103(66/37)  I:<5year(n:27)  II:5-10year(48)  III:>10 year(28) | I:34.2  II:38.1  III:49.1 | NM | I:2.5  II:7.0  III:19.7 | Hologic | L1-4, FN, radius | HLA-B27:92.2%  Disease duration<5 year OP:11%, 15%(hip, spine)  >10 year OP 29%, 4% (hip, spine)  DEXA: OP:24%, 14% and osteopenia:52%, 31%( hip, spine)  DEQCT OP:11% and Openia:44%(L)  pQCT OP:1% openia:16%(radius) | Patients with AS already have reduced BMD at the lumbar spine and the femoral neck early in the disease process. In later stage, OP ratio at hip increased but at LS did not increase |
| Lange *et al*[8] | AS: 84(53/31)  I: (10/17) II:(12/10) III:(12/3) IV:(19/1) | I:32 II:47 III:45  IV:56 | NM | I:9 II:20 III:21 IV:32 | Lunar | LS (0.9-1), total hip(1.6) | A high decrease in axial bone density could be verified in both initial and advanced stages of the disease (SE-QCT is better)  DXA: osteopenia in 5% and OP in 9.2%;  SE-QCT: osteopenia in 11.8% and osteoporosis in 30.3%  HLA-B27: 81.5-95%  VF: 10.7% | In stages of advanced ankylosis in the vertebral region, priority should be given to SE-QCT to detect bone loss, due to the selective measurement of trabecular and cortical bone |
| Incel *et al*[45] | AS:53(46/7) | 39.5 | 7:0 | 10.6 | Lunar | L2-4, FN | AS patients have lower BMD in LS end FN in both inactive and especially active patients.  Osteopenia is 78.3% in early AS  Osteopenia or OP is 63.3% in advanced AS. | Severe disease and concomitant urolithiasis may increase bone loss and fracture risk especially at the femur neck |
| Jun *et al*[28] | AS:68(68/0) | 30.7 | NA | 7.2 | Hologic | PA L2-4, left Prox Femur | BMD of LS and FN significantly lower than C  VF correlated with BMD femur.  VF:16.2% | Measurement of femur BMD may provide useful information to predict the risk of vertebral fractures in patients with AS |
| Kim *et al*[24] | AS:60(51/9) | 31.2 | NM | 5.5 | Hologic | AP L1-4(1), Right FN(1.2) | HLA-B27 83%  OP: LS 19%, FN 33%  Osteopenia: LS 37%, FN 41%  The patients with AS presented reduced BMD and T score at spine | About 74% of AS patients have reduced BMD  The imbalance between RANKL and OPG might be involved in the pathogenesis and clinical courses of osteoporosis in AS |
| Sarikaya *et al*[57] | AS:26(21/5) | 44.3 | 5:0 | NM | Hologic | Non dominant Hip(1), forearm(1) | Hip BMD values are lower in AS whereas radius BMD values are similar between 2 group  Hip Osteopenia or OP: 76.9% | OP at hip region may be due to localized effects of inflammatory activity or immobility rather than a systemic effect |
| Altindag *et al*[58] | AS:62(36/26) | 33.4 | NM | 5.7 | Hologic | AP L2-4, left FN | Lumbar and femoral neck BMD scores are significantly lower in AS  OP:32% osteopenia: 17.7% | Lumbar BMD scores negatively correlated with the length of disease duration in AS patients |
| Stupphann *et al*[15] | AS:21(10/11) | 51 | NM | 25.4 | Lunar | L1-4, total hip | TH: Osteopenia or OP 45% by DXA  LS: Osteopenia or OP 48% by QCT  QCT and DXA at proximal femur show a significant correlation but not at LS. | Activated CD4+ and CD8+ T cells contribute to the production of RANKL in the inflammatory bone-resorption |
| Ghozlani *et al*[23] | AS:80(67/13) | 38.9 | 13:0 | 10.8 | Lunar | AP L1-4, proximal F | OP:25%  VF:18.8%  OP is common in patients with AS and seems to be related to disease activity | Measuring BMD in early disease should include DXA in the spine and hip. In advanced disease, BMD evaluation should rely on hip DXA |
| Mermerci Baskan *et al*[25] | AS:100(75/25) | 39.9 | 25:0 | 10.5 | Hologic | AP L1-4 and Lat L2-3, FN | Thoracic VF:16%  Lumbar VF:3%  OP:32%  Acute phase reactant levels of the AS patients with OP are higher than the patients without OP | Vitamin D deficiency in AS may indirectly lead to osteoporosis by causing an increase in the inflammatory activity |
| Arends *et al*[22] | AS:128(93/35) | 41 |  | 14 | Hologic | AP L1-4, P F | BMD of the lumbar spine, measured by DXA, may be overestimated due to osteoproliferation in patients with advanced AS  HLA-B27:84%  VF:39%  Osteopenia or OP:57% | Bone turnover, inflammation, and low vitamin D levels are important in the pathophysiology of AS-related osteoporosis |
| Korczowska *et al*[59] | AS:66(66/0) | AS:51.6 | NA | 17.4 | DTX-200 or  ECLIPSE | Forearm and hip | Forearm: Osteopenia:54% and OP: 14%  Hip: Osteopenia: 51% and OP:5% | Accelerated loss of bone tissue is observed in patients with AS |
| Vasdev *et al*[29] | AS:80(80/0)  C:160(160/0) | 32.9 |  | 8.1 | Hologic | LS(1), hip(1) | In active and inactive patients, BMD is similar  OP:28.8% at LS and 11.5% at FN  VF:1.25%  HLA-B27:86% | OP is a significant complication in AS even in early disease, and more prevalent in the spine compared to femur  Spinal BMD is the most sensitive site for defining OP in AS |
| Weijden *et al*[4] | SpA:130(86/44)  -AS:72%  -uSpA:12%  -PsA:8%  -ReA:4% | 38 | 42:2 | 6.3 | Lunar | L2-4, left PF | Osteopenia:38%, OP:9%  HLA-B27:74%  No differences between group for distribution of the osteopenia and OP at hip or LS BMD | A high frequency of low BMD is found in patients with early SpA and it is associated with male gender and decreased functional capacity |
| Grazio *et al*[26] | AS: 80(46/34) | 52.3 | NM | 21.8 | Hologic | L2-4, left PF | HLA-B27 86%  at LS: OP:25% and osteopenia:20%  at FN OP:22.5 and osteopenia:47.4%  More patients with osteopenia at the lumbar spine had lower BASDAI score | Hip BMD seems to be more associated with disease activity and functional ability than BMD at the lumbar spine |
| Klingberg *et al*[27] | AS:204(117/87) | 50 | 42:45 | 24 | Hologic | AP L1-4(0.4), Lateral L2-4(0.6), left Hip, non-dominant radius | HLA-B27:87%  ≥50 y osteopenia: 43.6 and OP:20.8%  <50 y low BMD 4.9%  BMD at lateral LS was lower than AP and revealed more OP | OP and osteopenia is common in AS and associated with high disease burden. Lateral and volumetric lumbar DXA are more sensitive than AP DXA in detecting OP |
| Klingberg *et al*[60] | 204(117/87) | 50 | 42:45 | 24 | Hologic | AP L1-4, Lat L2-4, non dominant PF and forearm | BMD was significantly lower in the patients with VF.  HLA-B27: 87%  VF: 11.8% | BMD in the femoral neck, total hip, and estimated vertebral BMD show the strongest association with VF |
| Taylan *et al*[61] | AS:55(48/7) | AS:36 |  | 10 | Hologic | PA L2-4,  Left femur | BMD at proximal femur is lower but at lumbar spine was similar  HLA-B27:64.9% |  |
| van der Weijden *et al*[62] | SpA:113(75/38)  -AS :71% | 37 | 38:0 | 5.7 | Lunar | L2-4, left PF | In patients with VF, BMD at LS is lower than patients without VF  HLA-B27:75%  VF:15% | The VFs are associated with low BMD of the lumbar spine and with axial PsA |
| Akgol *et al*[30] | nr-axSpA: 46(32/14) | 31.4 | 14:0 | <3 | Hologic | LS (1), PF (3) | Patients with nr-axSpA have significant bone loss at the lumbar spine compared with patients with mLBP  Comparison of BMD in the nr-axSpA subgroups reveal that patients with inflammation had lower BMD at the LS and PF  HLA-B27: 60.8%  No VF | Inflammation on MRI is closely associated with low bone mass in patients who are in the very early stage of the disease |
| Briot *et al*[21] | SpA:332(174/158) | 33.8 | 151:7 | 1.6 | Hologic or Lunar | L1-4, FN, FT | Low BMD associated with presence of inflammatory lesions on MRI, ESR or CRP  HLA-B27 62.1%  Low BMD: 13%(M:88%) | Patients with early SpA had 13.0% low BMD and the main risk factor associated with low BMD was inflammation on MRI |
| Klingberg *et al*[9] | AS:69(69/0) | 49 | NA | 23 | Hologic | AP L1-4, lat L2-4, non dominant forearm and hip  HRpQCT: radius (0.3-3.9) and tibia (0.1-1.6)  QCT:L1-4 | The AS patients have lower vBMD in peripheral bone  Syndesmophytes are significantly associated with decreasing trabecular vBMD in lumbar spine. Estimated lumbar vBMD by DXA correlate with trabecular vBMD measured by QCT.  HLA-B27 94% | Male patients with AS have axial osteopenia. New bone formation cause false normal BMD at LS by DXA |
| Ulu *et al*[46] | AS:86(69/17) | AS:34.5 | NM | 11.7 | Hologic | PA L1-4, lat L2-4, femur | HLA-B27:66.3%  Sydesmophytes:37.2%  VF:28%  PA spine BMD similar with C  Lateral spine, hip BMD lower in AS  PA BMD higher in late stage AS than early stage.  FN, FT BMD lat spine BMD similar in two stage | Bone loss increase in AS  The BMD measurement at the lateral lumbar spine reflects bone loss and fracture risk better than PA spine and femoral measurements |

BMD: Bone mineral density; C: Control; DEQCT: Dual-energy quantitative computed tomography; DXA: Dual energy X-ray absorptiometry; F: Female; FN: Femur neck; HRpQCT: High-resolution peripheral quantitative computed tomography; M: Male; mLBP: Mechanic low back pain; NA: Not applicable; NM: Not mentioned; PA: Posteroanterir; PF: Proximal femur; pQCT: Peripheral quantitative computed tomography; SE-QCT: Single energy quantitative computed tomography; vBMD: Volumetric BMD.

**Table 2 Summary of the follow-up studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Sample size**  **(M/F)** | **Mean age (yr)** | **Menopausal status (pre:post)** | **Disease duration (yr)** | **Dexa machine** | **Dexa site (Coefficient variation%)** | **Follow-up (month)** | **Outcome** | **Conclusion** |
| Lee *et al*[17] | AS:14(14/0)  7early AS  7 advanced AS | 33.3  54.6 | NA | 5.4  27 | Hologic | LS (1), FN (1) | 15 | Baseline LS BMD measured by QCT decrease in both early (also by DXA) and advanced diseases and do not change significantly over 15 mo  HLA-B27 92.9% | AP LS DXA in late AS is less useful than QCT in determining the degree of osteopenia in late AS |
| Gratacos *et al*[6] | AS:34(27/7)  -active 14 (12/2)  -inactive 20(15/5) | -active: 33  -inactive: 31 | 7:0 | 7.5  5.3 | Lunar | LS (0.8), FN (2.3) | 19 | At the end of the follow-up period, patients with active AS show a significant reduction in bone mass in the LS (5%) and FN (3%) | Loss of bone mass only in patients with persistent active AS suggests that inflammatory activity plays a major role in the pathophysiology of the early bone loss |
| Maillefert *et al*[32] | AS:54(35/19) | 37.3 | 16:3 | 12,4 | Hologic | PA L2-4(2.8), left FN(4) | 24 | After 2 yr, BMD did not change at the LS and decreased at the FN  The change in BMD at FN was related to persistent systemic inflammation  HLA-B27 88.9%  VF:3.7% after 24 mo | Persistent inflammation may be an etiologic factor of bone loss in AS |
| Kaya *et al*[31] | AS:55(42/13)  Active:22  Inactive:33 | 35.8 | 13:0 | 11.1 | Lunar | AP L2-4 (2.1), PF (2.3) | 24 | Active AS have lower BMD at PF than inactive ones but LS BMD was similar  0.9% decrease in BMD at FN and increase at LS after follow-up, this change not different in active and inactive AS  active AS OP :PF:22.7% , LS:27.3%  Osteopenia: PF: 40.9%, LS: 31.8  inactive AS OP; PF: 3%, LS: 21,2%  Osteopenia; PF45.5%, LS33.3% | PF measurements seem to be less affected from disease-related new bone formation |
| Haugeberg *et al*[33] | SpA:30(15/15) | 31.1 | 15:0 | 6 | Lunar | AP L2-4 (2.3), both hip (2.8) and hand (1.1) | 12 | No significant reduction in BMD at hip, spine and hand is seen after 12 mo follow-up  Bone loss at PF is found to be associated with raised baseline CRP levels, baseline BMO of the SIJs on MRI  HLA-B27 56.7 | Bone loss in patients with SpA is a result of systemic inflammation and starts early in the disease process |
| Korkosz *et al*[18] | AS:19(19/0) | 45.6 | NA | 16.5 | Lunar | L2-4 (1.6-2.2), left hip  QCT:L1-5 | 120 | During the follow-up VF: 15.8%  In spine, trabecular BMC decrease by QCT whereas BMD increase by DXA | In AS patients, spinal trabecular bone density evaluated by QCT decrease over 10-yr follow-up and it is not related to baseline radiological severity of spinal involvement |

BMD: Bone mineral density; DXA: Dual energy X-ray absorptiometry; F: Female; FN: Femur neck; M: Male; NA: Not applicable; NM: Not mentioned; PA: Posteroanterir; PF: Proximal femur; QCT: Quantitative computed tomography.

**Table 3 Summary of the interventional studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Sample size**  **(M/F)** | **Mean age** | **Menopausal status pre:post** | **Disease duration (yr)** | **Dexa machine** | **Dexa site (Coefficient variation%)** | **Follow-up duration** | **Outcome** | **Conclusion** |
| Allali *et al*[39] | SpA:29(23/6) | 35 | 6:1 | 13 | Hologic | AP L2-4, left PF | 6 | A significant increase in BMD at the LS, total hip and trochanter is observed in patients with SpA treated with anti-TNF. | Benefit of anti-TNFα therapy on BMD in patients with SpA may be through an uncoupling effect on bone cells. |
| Briot *et al*[37] | SpA:19(17/2) | 40 | NM | 16.5 | Hologic | L2-4, left FT | 12 | After 1 year of treatment BMD increase at the spine and femur total. | Treatment with anti-TNFα in SpA is associated with an increase of BMD, which results from a decrease of bone resorption. |
| Biriot *et al*[41] | SpA106(80/26)  AS:87.8%  PsA:6.6% | 38 | NM | 16.5 | Hologic | L2-4, left PF | 24 | At 1 and 2 years of treatment, there is a significant gain in BMD at both lumbar spine and PF.  HLA-B27: 89%  Baseline : OP:28%, osteopenia:23% | This 2-year prospective study show a significant increase in BMD, in patients with SpA receiving anti-TNF-α treatment. |
| Visvanathan *et al*[40] | AS:279(225/54) | 40.3 | NM | 11.9 | NM | L1-4, PF | 24 | BMD at the spine and hip increase after anti-TNF therapy compared with placebo.  HLA-27 86.7% | Infliximab have positive effect on BMD over 2 years. |
| Kang *et al*[34] | AS:90(72/18) | 29.9  (onset age) | 18:0 | 8.2 | Lunar | AP L1-4, right PF | 36 | The most increase in BMD is observed at the spine and hip in the group treated with concurrent bisphosphonate and anti-TNF.  HLA-B27 97%  OP:36.7% | BMD increases more with the combination treatment (bisphosphonate and anti-TNF) and gain of bone mass is associated with the decrease in inflammation. |
| Arends *et al*[35] | AS:111(78/33) | 42.2 | NM | 16 | Hologic | AP L1-4, PF | 36 | LS and hip BMD significiantly increase compared to baseline after anti-TNFα theraphy.  HLA-B27: 81%  LS OP:9%, openia:34%  TF OP:2%, openia:37% | Three years of anti-TNF therapy results increase in bone formation in accordance with the continuous improvement in lumbar spinal BMD. |
| Dischereit *et al*[38] | RA: 18(3/15)  AS:16(9/7) | RA:62  AS:48 | NM | - | Lunar | AP L2-4 (1.5), FN(2) | 24 | At baseline in AS, osteopenia:50% and OP: 6.3%.  A stable peripheral BMD, significant increases in axial BMD, could be observed after 24 months of anti-TNFα therapy compared with baseline. | Anti-TNF therapy has favorable effects over osteoprotective pathways in patients with AS and RA. |
| Kang *et al*[36] | AS:63(52/11) | 36.8 | 11:2 | 8.6 | Prodigy | L1-4, right PF | 24 | BMD at LS and FT of patients receiving anti-TNF increase regularly over 2 years. TNF blocking therapy and the increase in SASSS are independently associated with increased BMD at lumbar spine.  HLA-B27: 87% | TNF inhibitors appear to be associated with increased SASSS scores and improvements in BMD. |

BMD: Bone mineral density; DXA: Dual energy X-ray absorptiometry; F: Female; FN: Femur neck; FT: Femur total; M: Male; NA: Not applicable; NM: Not mentioned; PA: Posteroanterir; PF: Proximal femur; QCT: Quantitative computed tomography; TNF: Tumor necrosing factor.

**Table 4 Variation of the bone formation and resorption markers**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Bone formation markers** | | **Bone resoption markers** | |
|  | **bALP** | **OC** | **CTX** | **DPD** |
| Borman *et al*[53] |  | Increased |  |  |
| Grisar *et al*[55] | Increased | Increased | Increased | Increased |
| Speden *et al*[7] | Decreased | Decreased |  | Increased |
| Sarikaya *et al*[57] |  | Decreased |  | Increased |
| Lee *et al*[17] |  | Normal |  | Normal |
| Altindag *et al*[58] | Increased | Decreased | Increased |  |
| Mermerci Baskan *et al*[25] | Normal |  |  |  |
| Acabes *et al*[51] |  |  | Normal | Increased |

bALP: Bone alkaline phosphatase, OC: Osteocalcin, CTX: C-terminal cross-linking telopeptide of type I collagen, DPD: Deoxypyridinoline.

**Figure 1 Flow chart.**

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Excluded based on abstract review if:

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6 Follow-up studies

(206 patients with SpA)

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