Osteoporosis in rheumatoid arthritis and ankylosing spondylitis

D. Vosse[1] and K. de Vlam[2]

[1]Division of Rheumatology, Department of Medicine, Maastricht University Medical Center, Maastricht, The Netherlands;
[2]Division of Rheumatology, Department of Musculoskeletal Science, University Hospital Leuven, Leuven, Belgium.

Debby Vosse, MD, PhD
Kurt de Vlam, MD, PhD

Please address correspondence to:
Dr Kurt de Vlam,
Division of Rheumatology
Department of Musculoskeletal Sciences,
University Hospitals Leuven,
Herestraat 49, B-3000 Leuven,
Belgium.
E-mail: Kurt.devlam@uz.kuleuven.ac.be

Received and accepted on July 29, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 55): S62-S67.

Key words: Osteoporosis, bone fragility, rheumatoid arthritis, ankylosing spondylitis.

Competing interests: none declared.

ABSTRACT

Bone is a target in many inflammatory rheumatic diseases, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). The generalized effect of inflammation on bone may result in a decreased quality of bone and is associated with an increased risk of fractures and deformities, both in RA and AS. RA is characterized by periarticular osteopenia, systemic osteoporosis and bone erosions. Periarticular osteopenia and bone erosions are mainly correlated with disease activity. Unlike postmenopausal osteoporosis, osteoporosis in RA is more characterised by marked loss of bone in the hip and the radius, while the axial bone is relatively preserved. In general, several cross-sectional studies documented a lower bone mineral density in patients with RA, with a two-fold increase in osteoporosis compared to age- and sex-matched controls and relates to an increased fracture risk. Several factors contribute to the increased risk: older age, little exercise, long-term use of corticosteroids, and high disability index.

AS is characterized by an increase in bone fragility due to reduced bone mineral density.

The reported prevalence of osteoporosis in AS patients varies largely. The large variation reflects the difficulties in assessing BMD in AS due to new bone formation. Bone fragility is also due to changes in structural properties resulting from inflammation-induced bone failure in the spine in combination with reduced capacity of shock absorption leading to vertebral fractures. Different types of spinal fractures in patients with AS are described, including wedging. Wedging vertebral fractures contribute to hyperkyphosis and impaired physical function. In contrast to RA , bone loss in AS is accompagnied by new bone formation. The pathophysiology of osteoporosis in RA and AS probably is fundamentally similar, but with different clinical phenotypes. The implications for therapeutically intervening in its occurrence and progression might be fundamentally different.

Introduction

Bone is a target in many inflammatory rheumatic diseases, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). The coexisting site-specific processes of bone and joint inflammation, bone destruction and bone proliferation point to a regulatory interplay between inflammatory processes and bone.

The rapid elucidation of cellular and molecular mechanisms underlying the interaction between inflammation and bone have resulted in the concept of 'osteoimmunology'(1-3). The interaction between the inflammatory cascade (immune system) and bone is characterized by a wide range of changes in bone remodeling not only at the site of inflammation, but also at skeletal sites more distantly from inflammation. The generalized effect of inflammation on bone may result in a decreased quality of bone and is associated with an increased risk of fractures and deformities, both in RA and AS (4).

RA: periarticular osteopenia, systemic osteoporosis and bone erosions

Rheumatoid arthritis is not only characterised by inflammation of the synovial tissue, but bone also is involved. RA is accompanied by three types of bone involvement: periarticular osteopenia, systemic osteoporosis and bone erosions

Periarticular osteopenia is one of the first radiographic signs of RA. It is most marked in early disease and is correlated with disease activity. The inflammatory process and immobilisation are the major determinants of bone mineral density (BMD) in the forearm. In cross-sectional studies the BMD at the hand is correlated to BMD in other sites such as hip and spine (5).

Systemic osteoporosis is prevalent in RA, but its magnitude is difficult to assess because most data are available from cross-sectional studies with varying inclusion criteria and a considerable diversity of methods assessing bone mineral density. Data concerning osteoporosis in men with RA are scarce. Several reports indicate that the fracture risk in patients with RA is increased. Several factors contribute to the increased risk: older age, little exercise, long-term use of corticosteroids, and high disability index.

Bone erosions are the radiographic hallmark of RA and reflect unfavourable prognosis. Erosions develop within the first months of the disease onset. The extent and severity reflect the cumulative disease activity and contribute to the disability of the disease. Within 6 months of disease onset, <50% of patients with early RA have radiographic erosions and almost 70% of the patients have lesions detected by MRI (6-8). Erosions on MRI may be accompanied by bone oedema. Aspiration of bone in these oedematous regions yielded CD34+ cells, potential osteoclast precursors (9).

AS: vertebral osteoporosis (fractures, wedging)

Inflammation in AS is characterized by subchondral bone marrow oedema, erosive lesions of the subchondral bone and eventually to subchondral new bone formation, bony bridging through the articular cartilage and ossification of the periarticular ligaments. The end stage is full bony fusion of the sacroiliac joints and ossification of the periarticular ligaments. Other inflammatory lesions are seen in the vertebral column, and may affect the apophyseal (posterior intervertebral) and costovertebral joints, the intervertebral discs, the superficial layers of the annulus fibrosis at their attachment to the corners of the vertebral bodies and the anterior, lateral and posterior intervertebral ligaments. Bone oedema is considered a sign of inflammatory activity and can cover limited or extensive parts of vertebrae. At the corners of the vertebral bodies it may be associated with marginal erosive lesions with adjacent subchondral oedema and sclerosis (Romanus lesion) (Fig. 1). At the periosteum of the vertebrae, erosions can be found, as well as signs of new periosteal intra-osseous bone formation which provides the typical picture of squaring of the vertebrae.

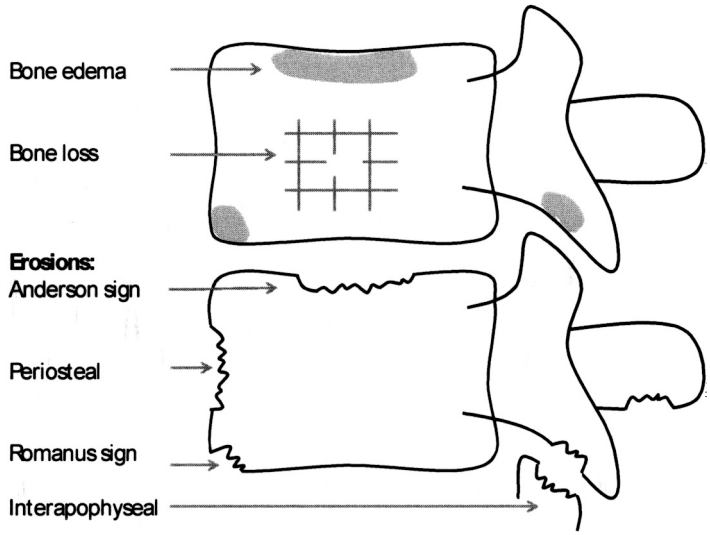

Fig. 1. Bone oedema, bone loss and erosion in AS.

Histologically, intra- and extra-osseous inflammation has been described. An extra-osseous granulomatous inflammatory pannus containing lymphocytes, plasma cells and multinucleated cells (osteoclasts) has been found in erosive lesions of the sacroiliac and spinal joints and at the entheses (at the corners of the vertebrae and at the periosteum) and ligamentous structures. Bone marrow oedema has been shown to be associated with histologically evident intra-osseous inflammation. Para-inflammatory osteoporosis has been described in the sacroiliac and interapophyseal joints, within the vertebrae and in the hip. Intra-osseous new bone formation may occur as woven bone repair remodeled to form mature lamellar bone. Extra-osseous new bone formation can occur in fibrous tissue without preceding cartilage formation, or by enchondral bone formation. Very recently it was proposed that a possible sequence of events in the regulation of new bone formation in AS is: first erosions at the site of inflammation, followed by repair reaction, followed by new bone formation (10). An alternative mechanism suggests that inflammation and repair in AS occur largely independent of one another (11).

Difficulties in assessment of osteoporosis in AS

The presence of syndesmophytes and other ectopic bone in AS may importantly jeopardize the reliability of BMD measurement, and this is why it is of limited value in order to establish poor bone quality in AS.

The place of ultrasound of the heel bone or CT scan is not yet clear, and not standardized.

Osteoporosis in RA

Unlike postmenopausal osteoporosis, osteoporosis in RA is more characterised by marked loss of bone in the hip and the radius, while the axial bone is relatively preserved. In general, several cross-sectional studies documented a lower bone mineral density in patients with RA, with a two-fold increase in osteoporosis compared to age- and sex-matched controls.

The frequency of osteoporosis in RA increases linearly with the Steinbrocker's index stage I to IV. RA patients with vertebral or femoral osteoporosis generally have longer disease duration, lower body mass index and greater disability compared to the non-osteoporotic RA controls.

Data about the prevalence of osteoporosis in men with RA are scarce. All studies reported at least a two-fold increase in overall prevalence, with a tendency for more femoral osteoporosis. The reduction of bone mineral density appears to be independent of serum testosterone (12, 13).

In general, osteoporosis in this population is also associated with increased rates of hip and vertebral fractures. Age, immobilisation, and low body mass index are confirmed independent risk factors for the development of osteoporosis, as seen for primary osteoporosis. Other factors in RA may also contribute, such as muscle wasting, glucocorticosteroids and disease duration. Interaction between several factors is not excluded: e.g. additional muscle wasting contributes to increased immobilisation.

The role of corticosteroids is still a matter of debate. Reviewed data from cross-sectional studies about dual-energy x-ray absorptiometry in RA patients treated with steroids are conflicting (4). Data from longitudinal population-based studies showed an increased risk for osteoporotic fractures. Patients with RA had an increased risk of fracture, which was most marked at the hip (RR 2.0, 95% confidence interval [95% CI] 1.8-2.3) and spine (RR 2.4, 95% CI 2.0-2.8). The increased risk is dose dependent for the oral steroids and is also attributable to the long-term use of oral glucocorticoids and the disease activity of RA (14).

The morbidity of generalised osteoporosis in RA patients is reflected in the increased fracture risk. Vertebral fracture risk is increased (15, 16). In a population-based case control study the risk for hip fracture is doubled for RA patients compared to non-RA patients (17).

The increase in overall fracture risk is correlated with postmenopausal status, mHAQ, and prednisone use. mHAQ was also associated with nonhip/nonspine fractures (18).

During the last decade, new targeted treatments with biological agents were initiated in patients with rheumatoid arthritis. All available TNF alpha blocking agents are quite successful in the prevention of formation of erosions. Denosumab, fully human monoclonal IgG2 antibody that binds RANKL, prevents also structural damage in patients treated with methothrexate (19). More generalised effects on bone are also reported. In patients with rheumatoid arthritis treated with infliximab, bone loss is arrested in the spine and hip, but not in the metacarpal cortical hand (20). Patients with RA can lose a substantial amount of vertebral strength over a relatively short period of time, but alendronate can prevent the loss of vertebral strength in patients with RA, primarily via its positive effect on the outer 2 mm of vertebral bone (21).

Osteoporosis in AS

Bone fragility due to reduced bone mineral density

The reported prevalence of osteoporosis in terms of low bone mineral density (BMD) in AS patients varies from 19% to 62% (22, 23). This large variation may reflect the difficulties in assessing BMD in AS due to spurious increase of BMD by the progressive appearance of syndesmophytes and ossifications. On the other hand, in patients with advanced AS, bone mineral density in the femoral neck is reduced, indicating osteoporosis due to an inflammatory process (24-26). Several authors using different imaging techniques like single and dual Energy x-ray Absorption (DXA), heel bone echography or quantitative computer tomography demonstrated low trabecular BMD and increased prevalence of axial low BMD even in mild and early forms of AS (25-28). In longitudinal studies it was shown that men with AS had an annual total bone mass loss of 2.2% (29).

Bone fragility due to changes in structural properties

Bone fragility is not only a result of reduced bone mineral density (BMD). There is increasing evidence that bone fragility also is due to changes in structural properties of bone that are not captured by measuring BMD (22, 29-32). Since inflammation in AS resides primarily in the spine, inflammation-induced bone failure in combination with reduced capacity of shock absorption may lead to vertebral fractures. Several studies mentioned a high prevalence of neurological complications, mostly followed by incomplete neurological recovery. This is in contrast to postmenopausal osteoporosis, senile osteoporosis and secondary osteoporosis due to other inflammatory diseases. A possible explanation could be that the (partially) ankylosed spine acts as a long bone which contributes to fractures in the horizontal plane and deformities, and consequently to hyperkyphosis of the upper part of the spine (33-37).

Increase in morphometric and clinical vertebral fractures, but not in peripheral fractures

In the light of this decreased quality of bone, it is likely that the risk of vertebral fractures is increased in AS (38). An increased relative risk on morphometric vertebral fractures of 7.6 among patients with AS as well as an increased risk of clinical vertebral fractures (CVF), is described. Strikingly, the risk for forearm and hip fracture was not found to be increased (39). This suggests a more local effect on bone, in contrast with RA, in which the inflammatory effects are more systemic. The reported prevalence of CVF varied widely (between 10 and 17%), but has not been assessed in a systematic manner (25, 33, 34, 38, 40, 41).

Overall, there are three different types of spinal fractures in patients with AS: simple compression fractures of the vertebral body, similar to those found in postmenopausal osteoporosis (Fig. 2); fractures of the vertebral body, the components of the dorsal arch and fractures within extra skeletal newly formed bone (Fig. 3).

Fractures, hyperkyphosis and impaired physical function

Besides the burden of CVF's, hyperkyphosis of the upper part of the spine is a frequent clinical problem among patients with ankylosing spondylitis (AS) (42-44). The prominent position of the head and neck may result in functional and psychological impairment (45). In the prevalence cohort of patients with AS [Outcome in AS International Study (OASIS) cohort] with a mean disease duration of 9.4 years, 49% of the patients have some degree of hyperkyphosis, expressed as an Occiput-to-Wall Distance (OWD) of more than 0 cm (46). Several studies indicate that wedging vertebral fractures contribute to hyperkyphosis (37, 41, 47). Three independent significant contributory

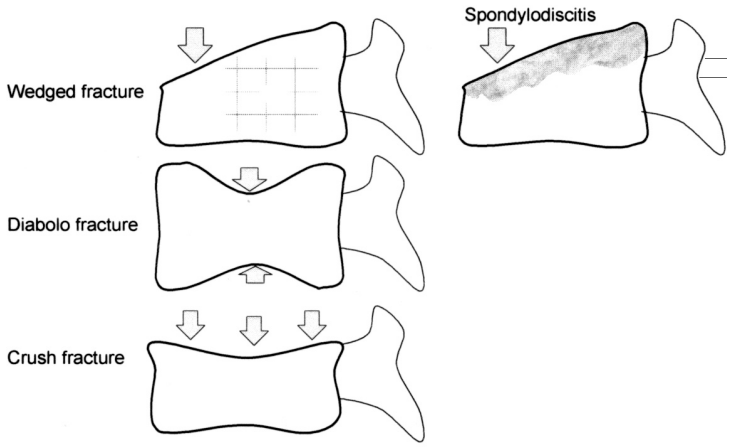

Fig. 2. Vertebral body fractures

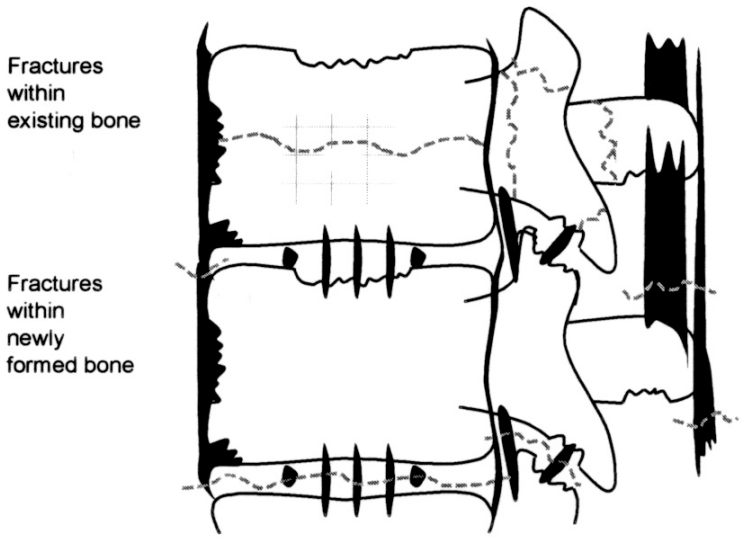

Fig. 3. Fractures in bone and calcified ligaments in AS

factors to hyperkyphosis include: structural damage of the spine, wedging of thoracic vertebrae, and cross-sectional disease activity (48). It is likely that wedging deformities are a direct result of inflammation-driven bone failure, *i.e.* of osteoporosis.

Relation between bone and cartilage markers and osteoporosis/damage

Another method to assess bone quality is measurement of bone metabolism by markers of bone resorption (type 1 collagen (CTX-I)) and of cartilage destruction (type II collagen (CTX II)). For RA and psoriatic arthritis (PsA), knowledge about the effects of inflammation on bone has been rapidly increased by elucidating the role of osteoclasts in causing bone destruction, as well as their inflammatory triggers (49-51). To date, however, the precise relationship between inflammation and bone formation in AS remains insufficiently understood, and there is increasing evidence that inflammation and new bone formation in AS are at least partly uncoupled. Notwithstanding these pathophysiological uncertainties, the concept of impaired bone quality in AS is broadly accepted.

In RA, radiological damage resulting from chronic inflammation includes cartilage destruction and bone erosion. Specific biochemical markers of type I collagen degradation (CTX-I) (reflecting bone) and type II collagen degradation (CTX II) (reflecting cartilage) could predict radiographic progression in RA (52-54). In AS the pathophysiological processes underlying radiological progression are unclear. While excessive bone formation (syndesmophytes) is most characteristic of AS, erosions and destruction of "vertebral units" (vertebral bone plus intervertebral disc) may occur. A few cross-sectional studies have analysed biochemical markers of bone turnover and have reported conflicting data, but there seems to be increased bone resorption (55, 56). Only two studies have addressed markers of cartilage turnover, but the association with radiological damage or BMD was not investigated (57, 58). A recent study (59) suggested that bone resorption, reflected by CTX-I, and extra-osseous new bone formation, reflected by modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and associated with cartilage damage (CTX-II), are probably different aspects of structural changes in AS.

Therefore, AS is characterized by bone and cartilage degradation. The former reflects the systemic inflammatory effects on bone density and can be influenced by TNF-α blocking agents, while the latter is somehow associated with syndesmophyte formation, which is not influenced by anti-inflammatory treatment modalities. This underlines the suggestion that bone degradation and new bone formation are separate processes in AS.

Conclusion

Osteoporosis in RA and AS is well established and clinically relevant because of the relationship between damage (fractures/hyperkyphosis) and physical function. The pathophysiology of osteoporosis in RA and AS is probably fundamentally similar, but with different clinical phenotypes. The implications for therapeutically intervening in its occurrence and progression might be fundamentally different.

References

1. WALSH NC, CROTTI TN, GOLDRING SR, GRAVALLESE EM: Rheumatic diseases: the effects of inflammation on bone. *Immunol Rev* 2005; 208: 228-51.
2. PETTIT AR, WALSH NC, MANNING C, GOLDRING SR, GRAVALLESE EM: RANKL protein is expressed at the pannus-bone interface at sites of articular bone erosion in rheumatoid arthritis. *Rheumatology* (Oxford). 2006; 45: 1068-76.
3. DIARRA D, STOLINA M, POLZER K *et al.*: Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007; 13: 156-63.

4. SINIGAGLIA L, VARENNA M, GIRASOLE G, BIANCHI G: Epidemiology of osteoporosis in rheumatic diseases. *Rheum Dis Clin North Am* 2006; 32: 631-58.
5. HARRISON BJ, HUTCHINSON CE, ADAMS J, BRUCE IN, HERRICK AL: Assessing periarticular bone mineral density in patients with early psoriatic arthritis or rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 1007-11.
6. VAN DER HEIJDE DMFM: Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol* 1995; 34 (Suppl. 2): 74-8.
7. MCQUEEN FM, STEWART N, CRABBE J *et al*.: Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. *Ann Rheum Dis* 1998; 57: 350-6.
8. MCGONAGLE D, CONAGHAN PG, O'CONNOR P *et al*.: The relationship between synovitis and bone changes in early untreated rheumatoid arthritis: a controlled magnetic resonance imaging study. *Arthritis Rheum* 1999; 42: 1706-11.
9. BOYLE WJ, SIMONET WS, LACEY DL: Osteoclast differentiation and activation. *Nature* 2003; 423: 337-42.
10. SIEPER J, APPEL H, BRAUN J, RUDWALEIT M: Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. *Arthritis Rheum* 2008; 58: 649-56.
11. LORIES RJ, LUYTEN FP, DE VLAM K: Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. *Arthritis Res Ther* 2009; 11: 221.
12. TENGSTRAND B, HAFSTRÖM I: Bone mineral density in men with rheumatoid arthritis is associated with erosive disease and sulfasalazine treatment but not with sex hormones. *J Rheumatol* 2002; 29: 2299-305.
13. HAUGEBERG G, UHLIG T, FALCH JA, HALSE JI, KVIEN TK: Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum* 2000; 43: 2776-84.
14. VAN STAA TP, GEUSENS P, BIJLSMA JW, LEUFKENS HG, COOPER C: Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 3104-1.
15. PEEL NF, MOORE DJ, BARRINGTON NA, BAX DE, EASTELL R: Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1995; 54: 801-6.
16. ØRSTAVIK RE, HAUGEBERG G, MOWINCKEL P *et al*.: Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. *Arch Intern Med* 2004; 164: 420-5.
17. HUUSKO TM, KORPELA M, KARPPI P, AVIKAINEN V, KAUTIAINEN H, SULKAVA R: Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland. *Ann Rheum Dis* 2001; 60: 521-2.
18. COULSON KA, REED G, GILLIAM BE, KREMER JM, PEPMUELLER PH: Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the consortium of rheumatology researchers of North American Registry. *J Clin Rheumatol* 2009 (in press).
19. COHEN SB, DORE RK, LANE NE *et al*.: Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum* 2008; 58: 1299-309.
20. VIS M, HAVAARDSHOLM EA, HAUGEBERG G *et al*.: Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkappaB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 1495-9.
21. MAWATARI T, MIURA H, HAMAI S *et al*.: Vertebral strength changes in rheumatoid arthritis patients treated with alendronate, as assessed by finite element analysis of clinical computed tomography scans: a prospective randomized clinical trial. *Arthritis Rheum* 2008; 58: 3340-9.
22. BESSANT R, KEAT A: How should clinicians manage osteoporosis in ankylosing spondylitis? *J Rheumatol* 2002; 29: 1511-9.
23. GRAN JT, HUSBY G: Clinical, epidemiological, and therapeutic aspects of ankylosing spondylitis. *Curr Opin Rheumatol* 1998; 10: 292-8.
24. DEVOGELAER JP, MALDAGUE B, MALGHEM J, NAGANT DE DEUXCHAISNES C: Appendicular and vertebral bone mass in ankylosing spondylitis. A comparison of plain radiographs with single- and dual-photon absorptiometry and with quantitative computed tomography. *Arthritis Rheum* 1992; 35: 1062-7.
25. WILL R, PALMER R, BHALLA AK, RING EFJ, CALIN A: Osteoporosis in early ankylosing spondylitis: a primary pathologic event? *Lancet* 1989; 2: 1483-5.
26. COOPER C, CARBONE L, MICHET CJ, ATKINSON EJ, O'FALLON WM, MELTON LJ 3RD: Fracture risk in patients with ankylosing spondylitis: a population based study. *J Rheumatol* 1994; 21: 1877-82.
27. LEE YS, SCHLOTZHAUER T, OTT SM *et al*.: Skeletal status of men with early and late ankylosing spondylitis. *Am J Med* 1997; 103: 233-41.
28. DONNELLY S, DOYLE DV, DENTON A, ROLFE I, MCCLOSKEY EV, SPECTOR TD: Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Ann Rheum Dis* 1994; 53: 117-21.
29. BRONSON WD, WALKER SE, HILLMAN LS, KEISLER D, HOYT T, ALLEN SH: Bone mineral density and biochemical markers of bone metabolism in ankylosing spondylitis. *J Rheumatol* 1998; 25: 929-35.
30. CHAVASSIEUX P, SEEMAN E, DELMAS PD: Insights into material and structural basis of bone fragility from diseases associated with fractures. How determinants of the biomechanical properties of bone are compromised by disease. *Endocr Rev* 2007; 28: 151-64.
31. DEODHAR AA, WOOLF AD: Bone mass measurement and bone metabolism in rheumatoid arthritis: a review. *Br J Rheumatol* 1996; 35: 309-22.
32. GRATACOS J, COLLADO A, PONS F *et al*.: Significant loss of bone mass in patients with early, active ankylosing spondylitis: a follow up study. *Arthritis Rheum* 1999; 42: 2319-24.
33. MITRA D, ELVINS DM, SPEDEN DJ, COLLINS AJ: The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. *Rheumatology* 2000; 39: 85-9.
34. HUNTER T, DUBO HIC: Spinal fractures complicating ankylosing spondylitis. A long-term follow-up study. *Arthritis Rheum* 1983; 26: 751-9.
35. GENANT HK, WU CY, KUIJK VAN C, NEVITT MC: Vertebral fracture assessment using a semi quantitative technique. *J Bone Miner Res* 1993; 8: 1137-48.
36. NGUYEN HV, LUDWIG S, GELB D: Osteoporotic vertebral burst fractures with neurologic compromise. *J Spin Dis Techn* 2003; 16: 10-9.
37. VOSSE D, FELDTKELLER E, ERLENDSSON J, GEUSENS P, VAN DER LINDEN S: Clinical vertebral fractures in patients with Ankylosing Spondylitis. *J Rheumatol* 2004; 31: 1981-5.
38. RALSTON SH, URQUHART GDK, BRZESKI M, STURROCK RD: Prevalence of vertebral com- pression fractures due to osteoporosis in ankylosing spondylitis. *BMJ* 1990; 300: 563-5.
39. VOSSE D, LANDEWÉ R, VAN DER HEIJDE D, VAN DER LINDEN S, VAN STAA TP, GEUSENS P: Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case control study. *Ann Rheum Dis* 2008 Dec 9. [Epub ahead of print].
40. REID DM, NICOLL JJ, KENNEDY NJS *et al*.: Bone mass in ankylosing spondylitis. *J Rheumatol* 1986; 13: 932-5.
41. GEUSENS P, VOSSE D, VAN DER HEIJDE D *et al*.: High prevalence of thoracic vertebral deformities and discal wedging in ankylosing spondylitis patients with hyperkyphosis. *J Rheumatol* 2001; 28: 1856-61.
42. CARETTE S, GRAHAM D, LITTLE H, RUBENSTEIN J, ROSEN P: The natural disease course of ankylosing spondylitis. *Arthritis Rheum* 1983; 26: 186-90.
43. WILKINSON M, BYWATERS EGL: Clinical features and course of ankylosing spondylitis. *Ann Rheum Dis* 1958; 17: 209-16.
44. SPENCER DG, PARK WM, DICK HM, PAPAZOGLOU SN, BUCHANAN WW: Radiological manifestations in 200 patients with ankylosing spondylitis: correlation with clinical features and HLA-B27. *J Rheumatol* 1979; 6: 305-15.
45. MCMASTER MJ: Osteotomy of the cervical spine in ankylosing spondylitis. *J Bone Joint Surg* (Br) 1997; 79: 197-203.
46. SPOORENBERG A, VAN DER HEIJDE D, DE KLERK E *et al*.: A comparative study of the usefulness of the Bath Ankylosing Spondylitis Functional Index and the Dougados Functional Index in the assessment of ankylosing spondylitis. *J Rheumatol* 1999; 26: 961-5.
47. HUNTER T, DUBO HIC: Spinal fractures complicating ankylosing spondylitis. A long-term follow-up study. *Arthritis Rheum* 1983; 26: 751-9.
48. VOSSE D, VAN DER HEIJDE DM, LANDEWÉ R *et al*.: Determinants of hyperkyphosis in patients with Ankylosing Spondylitis. *Ann Rheum Dis* 2006; 65: 770-4.

49. GARNERO P, LANDEWÉ R, MAARTEN B *et al*.: Association of baseline levels of markers of bone and cartilage degradation are associated with long-term progression of joint damage in patients with early rheumatoid arthritis: the Cobra study. *Arthritis Rheum* 2002; 46: 2847-56.
50. LANDEWÉ RB, GEUSENS P, VAN DER HEIJDE DM, BOERS M, VAN DER LINDEN SJ, GARNERO P: Arthritis instantaneously causes collagen type I and type II degradation in patients with early rheumatoid arthritis: a longitudinal analysis. *Ann Rheum Dis* 2006; 65: 40-4.
51. RITCHLIN CT, HAAS-SMITH SA, LI P, HICKS DG, SCHWARZ EM: Mechanisms of TNF-α and RANKL mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003; 111: 821-31.
52. GARNERO P, GINEYTS E, CHRISTGAU S, FINCK B, DELMAS PD: Association of baseline levels of urinary glucosyl-galactosyl-pyridinoline and type II collagen C-Telopeptide are associated with progression of joint destruction in patients with early rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 21-30.
53. GARNERO P, LANDEWÉ R, MAARTEN B *et al*.: Association of baseline levels of markers of bone and cartilage degradation are associated with long-term progression of joint damage in patients with early rheumatoid arthritis: the Cobra study. *Arthritis Rheum* 2002; 46: 2847-56.
54. LANDEWÉ RB, GEUSENS P, VAN DER HEIJDE DM, BOERS M, VAN DER LINDEN SJ, GARNERO P: Arthritis instantaneously causes collagen type I and type II degradation in patients with early rheumatoid arthritis: a longitudinal analysis. *Ann Rheum Dis* 2006; 65: 40-4.
55. GARNERO P, DELMAS PD: Noninvasive techniques for assesing skeletal changes in inflammatory arthritis: bone biomarkers. *Curr Opin Rheumatol* 2004; 16: 428-34.
56. TOUSSIROT E, RICARD-BLUM S, DUMOULIN G, CEDOZ JP, WENDLING D: Relationship between urinary pyridinium cross-links, disease activity and disease subsets of ankylosing spondylitis. *Rheumatology* 1999; 38: 21-37.
57. KIM TH, STONE M, PAYNE U *et al*.: Cartilage biomarkers in ankylosing spondylitis relationship to clinical variables and treatment response. *Arthritis Rheum* 2005; 52: 885-91.
58. MAKSYMOWYCH WP, POOLE AR, HIEBERT L *et al*.: Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis. *J Rheumatol* 2005; 32: 1911-7.
59. VOSSE D, LANDEWÉ R, GARNERO P, VAN DER HEIJDE D, VAN DER LINDEN S, GEUSENS P: Association of markers of bone- and cartilage degradation with radiological changes at baseline and after 2 years follow-up in patients with ankylosing spondylitis. *Rheumatol* 2008; 47: 1219-22.