Using hand bone mass measurements to assess progression of rheumatoid arthritis

Mari Hoff and Glenn Haugeberg

Ther Adv Musculoskel Dis
(2010) 2(2) 79–87
DOI: 10.1177/1759720X10362297

Abstract: In rheumatoid arthritis (RA) bone involvement presents as joint erosions in addition to generalized and periarticular osteoporosis. Joint erosions on radiographs of the hands and feet are considered to be the gold standard to evaluate progression of bone and joint damage in RA, even though erosions on radiographs are not used as a marker of early bone involvement. Periarticular bone loss seen on radiographs may be the first sign of bone involvement in RA. Over the last decade there has been an increased awareness of the importance of early aggressive treatment in RA, leading to a need for methods which can identify bone involvement in the early stages of RA. As inflammatory bone loss, especially at the hand, has been shown to occur early in RA, quantitative measures of hand bone loss have been proposed as an outcome measure for the detection of bone involvement. In this review article we present data supporting the hypothesis that both erosions and osteoporosis in RA occur as a result of the same pathophysiological mechanisms activating the osteoclast. Furthermore the role of hand bone loss as an early marker of inflammatory bone involvement, a predictor of subsequent radiographic joint damage and a response variable to anti-inflammatory treatment is discussed.

Keywords: erosions, osteoporosis, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease characterized by synovitis and destruction of cartilage and bone in joints, especially the small joints of the hands and feet [Klareskog *et al.*, 2009; Feldmann *et al.*, 1996]. The prevalence of RA is about 0.5–1.0% [Alamanos *et al.*, 2006; Kvien *et al.*, 1997] with an annual incidence of 25–50/100,000 [Alamanos *et al.*, 2006; Uhlig *et al.*, 1998]. This makes RA one of the most frequent inflammatory rheumatic diseases. The impact of the disease is significant for both the individual and society as a whole, as the disease is accompanied by increased morbidity, disability and even mortality [Young and Koduri, 2007].

While disability in early RA is driven by inflammation, destruction of bone is the main reason for disability in established RA [Klareskog *et al.*, 2009; Smolen *et al.*, 2007; van der Heijde, 2001]. Prevention of bone damage in RA is thus of major importance in avoiding future disability. Bone involvement in RA presents as erosions, generalized osteoporosis and periarticular (juxtaarticular) osteoporosis [Sambrook, 2000]. The prevalence of generalized osteoporosis has been found to be doubled in RA patients compared with the normal population [Haugeberg *et al.*, 2000b], and both hip and vertebral fractures occur more frequently in RA patients than in the normal population [van Staa *et al.*, 2006; Orstavik *et al.*, 2004a, 2004b; Huusko *et al.*, 2001]. In the 1987 American College of Rheumatology (ACR) revised criteria of RA, both erosions and periarticular osteoporosis are defined as typical hallmarks of bone involvement in RA [Arnett *et al.*, 1988]. To date, conventional radiographs have been considered to be the gold standard to evaluate the progression of bone and joint damage in RA [Boini and Guillemin, 2001; van der Heijde, 1996]. However, erosions may not appear on radiographs early in the disease and periarticular osteoporosis may occur before the erosions are visible [Brook and Corbett, 1977; Bywaters, 1960]. Periarticular osteoporosis cannot be quantified based on the visual impression seen on radiographs and has to be detected by quantitative bone mass measures [Bottcher *et al.*, 2006c; Jergas *et al.*, 1994].

Correspondence to:
Glenn Haugeberg, MD, PhD
Sørlandet Hospital HF, Department of Rheumatology, Service box 416, 4604 Kristians and S, Norway
glenn.haugeberg@sshf.no

Mari Hoff, MD, PhD
Department of Rheumatology, St Olavs Hospital, University Hospital of Trondheim, Norway,
and Norwegian University of Science and Technology, Trondheim, Norway

In this article we review the mechanism for bone involvement in RA, methods for quantitative assessment of hand bone density and discuss the ability of quantitative hand bone measures to capture bone involvement and the progression of bone damage in RA.

Mechanism for bone involvement in rheumatoid arthritis

Results from animal and human studies support the hypothesis that both erosions and osteoporosis in RA are results of the same inflammatory pathophysiological mechanism involving the osteoclast [Cohen *et al.*, 2008; Jarrett *et al.*, 2006; Goldring and Gravallese, 2004; Herrak *et al.*, 2004; Sims *et al.*, 2004; Redlich *et al.*, 2002; Gravallese *et al.*, 1998]. The important role of the osteoclast was demonstrated in an animal study where transgenic mice that expressed human tumour necrosis factor (TNF)-α and developed a severe destructive arthritis were crossed with mice lacking osteoclasts. The resulting mutant mice developed arthritis, but were fully protected against bone destruction [Redlich *et al.*, 2002]. Further, suppression of the osteoclast by the potent bisphosphonate zoledronic acid has indicated a reduction of erosions both in animal studies [Goldring and Gravallese, 2004; Herrak *et al.*, 2004; Sims *et al.*, 2004] and in human studies [Jarrett *et al.*, 2006].

The activation and development of osteoclasts depends on stimulation from receptor activator of nuclear factor-κ ligand (RANKL). RANKL is a member of the TNF ligand superfamily of cytokines and binds to the receptor activator of nuclear factor-κ (RANK) [Gravallese, 2002]. The interaction of this receptor–ligand pair is essential for osteoclastogenesis [Schett *et al.*, 2005]. Mice with a serum transfer model of arthritis that were lacking RANKL were protected against bone destruction [Pettit *et al.*, 2001]. Osteoprotegerin (OPG) is a naturally occurring decoy receptor for RANKL. The ratio of RANKL/OPG determines the degree of osteoclast-mediated bone resorption [Gravallese, 2002; Green and Deodhar, 2001]. A new antibody against RANKL, denosumab, has been found to reduce the development of erosions in RA, but had no influence on the disease activity [Cohen *et al.*, 2008].

The expression of RANKL is stimulated by pro-inflammatory cytokines such as TNF-α, interleukin-1 (IL-1), IL-6, IL-16, IL-17 and macrophage colony-stimulating factor (M-CSF) [Gravallese, 2002; Green and Deodhar, 2001]. It has also been suggested that TNF-α may have the ability to bind directly to osteoclast precursors through TNF-α receptor and stimulate the osteoclast formation [Schett, 2007; Lam *et al.*, 2000]. This dual effect of TNF-α on the osteoclast may explain why treatment with anti-TNF therapy reduces hand bone loss and erosions independently of disease activity, in contrast to methotrexate [Hoff *et al.*, 2009d; Emery *et al.*, 2009; Smolen *et al.*, 2009].

Recently, interest has grown in the osteoblast in inflammatory arthritis. An increased bone resorption should normally be coupled to an increased bone formation by the osteoblast, but this is not the case in RA. Studies suggest that the inflammation may suppress the bone formation activity of the osteoblast. The osteoblast is activated by the Wnt (wingless protein) pathway which also leads to an induction of OPG and thus reduces the activity of the osteoclast [Schett, 2009; Schett *et al.*, 2008]. TNF-α seems to induce Dickkopf 1 (DKK1) which inhibits Wnt. This further leads to a down-regulation of both the osteoblast and OPG, resulting in an inhibition of the bone formation. In this manner RA inflammation also seems to inhibit the osteoblast, which gives an additive negative effect of inflammation on bone [Garnero *et al.*, 2008; Schett *et al.*, 2008].

Measurements of bone density

As mentioned in the introduction, hand bone loss cannot be quantified or graded sufficiently on radiographs. It is estimated that bone loss less than 20–40% cannot be detected on plain radiographs [Bottcher *et al.*, 2006c; Jergas *et al.*, 1994]. Several devices have been developed for quantitative assessments of bone density [Njeh and Genant, 2000], e. g. quantitative ultrasound (US) [Njeh *et al.*, 1997], quantitative computer tomography (qCT) [Cann, 1988], dual energy X-ray absorptiometry (DXA) [Blake and Fogelman, 1997] and radiogrammetry [Rosholm *et al.*, 2001]. Owing to their feasibility and precision, DXA and digital X-ray radiogrammetry (DXR) are the two methods most frequently used to study inflammatory osteoporosis in RA (Table 1).

DXA is considered as the gold standard for the detection and management of osteoporosis [Kanis *et al.*, 2008]. The method is based on the known differences in the relative attenuation of high-energy and low-energy X-rays by bone and

Table 1. Selected studies on hand bone loss in patients with rheumatoid arthritis (numbers of participants in parenthesis).

Study	Diagnosis	Disease duration	DXR-BMD % change	DXR-MCI % change	DXA-BMC % change	DXA-BMD % change
Daragon *et al.* [2001]	RA (15)/ORD (15)	<0.5 yr			1 yr: –2.2/–0.3	1 yr: –2.6/–0.4
Deodhar *et al.* [2003]	RA (29)	<2 yr			1 yr: –5.5 2 yr: –7.5 3 yr: –9.8 5 yr: –10.0	
Jensen *et al.* [2004]*	RA (51)/ORD (21)	2 yr	2 yr: –5.0/–2.0			2 yr: NS
Stewart *et al.* [2004]	RA (24) Erosive/ non-erosive	<1 yr	1 yr: –7.1/–0.2	1 yr: –8.1–1.0		1 yr:–5.4–1.0
Haugeberg *et al.* [2005]	RA (95) Prednisolone users/non-users	<2 yr	2 yr: –3.6/–7.1			
Böttcher *et al.* [2005b]	RA (258)	<1 yr	1 yr: –10.7 6 yr: –32.1	1 yr: –14.3 6 yr: –33.3		
Haugeberg *et al.* [2006]	RA (13)/ORD (19)/ arthralgia (42)	<1 yr				1 yr: –4.3/ –0.5/–0.9
Hoff *et al.* [2007]*	RA (215)	9 yr	2 yr: –0.9	2 yr: –1.2		2 yr:0.0
Hoff *et al.* [2009a]*	RA (136)	<4 yr	1 yr: –1.7			
Güler-Yuksel *et al.* [2009]	RA (218)	<2 yr	1 yr: –1.4			

*Median change, otherwise mean change.
DXR, digital X-ray radiogrammetry; BMD, bone mineral density; MCI, metacarpal cortical index; DXA, dual energy X-ray absorptiometry; BMC, bone mineral content; yr, years; RA, rheumatoid arthritis; ORD, other rheumatic disease; NS, nonsignificant.

soft tissue [Blake and Fogelman, 1997]. Software to measure hand DXA is now commercially available. Both bone mineral density (BMD) and bone mineral content (BMC) can be measured, but BMD has been preferred due to better precision [Murphy *et al.*, 2008; Daragon *et al.*, 2001]. DXA-BMD can be calculated from both the whole hand and regions of interest around the joints [Alenfeld *et al.*, 2000; Deodhar *et al.*, 1994]. Even though measures of bone loss around the joints shows larger values of bone loss, the method for measuring the whole hand is more feasible and the precision is considerably better than for regions around finger joints [Murphy *et al.*, 2008; Daragon *et al.*, 2001; Alenfeld *et al.*, 2000].

DXR is a computer version of the traditional technique of radiogrammetry [Barnett and Nordin, 1960] and measures cortical BMD from defined regions of interest in the second, third and fourth metacarpal bone. The final BMD estimate is defined as:

$$\text{DXR-BMD} = c \times \text{VPA}_{\text{comb}} \times (1 - p)$$

[Rosholm *et al.*, 2001; Jorgensen *et al.*, 2000], where c is a density constant, VPA is volume per area and p is porosity. Porosity is defined as the percentage of cavities not occupied by mineral matter and is usually in the range of 2–4%.

The DXR method also measures DXR-metacarpal cortical index (MCI), defined as the combined cortical thickness divided by the bone width. DXR-MCI is a relative bone measure and less dependent on bone size and bone length than DXR-BMD [Hyldstrup and Nielsen, 2001; Nielsen, 2001]. DXR can be analysed both from conventional X-rays [Bottcher *et al.*, 2004; Rosholm *et al.*, 2001] or from digitized X-rays by the dxr-online system (Sectra, Linköping) [Guler-Yuksel *et al.*, 2009].

A limitation of the DXR method is that BMD or MCI cannot be measured in patients with severe deformities, as the system does not recognize the regions of interest in the metacarpal bones. Further, the method does not allow DXR to be measured in patients with metal implants in hands. These limitations of DXR exclude analysis of patients with severe disease.

The precision has been shown to be good for both the DXA and the DXR method. The *in-vivo* short-term precision expressed as coefficient of variance (CV%) for hand DXA-BMD has been calculated to be 0.8–1.4% for the whole hand [Haugeberg *et al.*, 2007; Berglin *et al.*, 2003; Daragon *et al.*, 2001; Alenfeld *et al.*, 2000] and 0.9–4.5% for regions around the joints [Murphy *et al.*, 2008; Harrison *et al.*, 2002; Daragon *et al.*, 2001; Alenfeld *et al.*, 2000].

For DXR-BMD using conventional radiographs the CV has been found to be 0.28–0.46% and for DXR using digitized radiographs (dxr-online) 0.14–0.30% [Hoff *et al.*, 2009b]

Periarticular *versus* generalized osteoporosis

The small joints in hands and feet are the most frequently involved joints in the inflammatory disease process in RA [Arnett *et al.*, 1988]. Thus, bone density measures of the hand are recommended for assessment of periarticular osteoporosis in RA whereas bone density measures at, for example, the spine and hip are used as measurement sites for generalized osteoporosis.

Studies support that hand bone loss measured by DXA and DXR takes place in early RA [Haugeberg *et al.*, 2006; Jensen *et al.*, 2004; Deodhar *et al.*, 2003], even in the undifferentiated stage of the RA disease process [Haugeberg *et al.*, 2006; Jensen *et al.*, 2004]. Patients with RA have significantly lower hand DXA-BMD compared with healthy controls [Alenfeld *et al.*, 2000] and patients suffering from psoriatic arthritis [Harrison *et al.*, 2002]. In longitudinal studies, RA patients have been found to lose more hand BMD compared both with patients with other rheumatic diseases [Haugeberg *et al.*, 2006; Jensen *et al.*, 2004; Daragon *et al.*, 2001] and with healthy controls [Deodhar *et al.*, 1995].

Studies also indicate that hand bone loss in early RA occurs more rapidly than bone loss at the hip and spine [Guler-Yuksel *et al.*, 2009; Haugeberg *et al.*, 2006; Devlin *et al.*, 1996]. Radiographic joint damage has been shown to be more strongly correlated with low hand DXR-BMD than DXA-BMD at the hip and spine [Bottcher *et al.*, 2004; Haugeberg *et al.*, 2004]. These studies suggest that whereas the prolonged course of RA, including immobility and the use of corticosteroids, may be more associated with generalized bone loss [Haugeberg *et al.*, 2000a], the effect of inflammation may have a greater impact on hand bone loss [Haugeberg *et al.*, 2006].

Predictors of hand bone loss and the association with inflammation

The associations between disease factors and hand bone loss in RA has been studied [Boyesen *et al.*, 2009; Guler-Yuksel *et al.*, 2009; Hoff *et al.*, 2007, 2009a, 2009e; Haugeberg *et al.*, 2006; Deodhar *et al.*, 1995, 2003]. Hand bone loss both detected by DXA (BMC and BMD) and DXR (BMD and MCI) has been found to be correlated with high baseline C-reactive protein (CRP) and DAS 28 [Guler-Yuksel *et al.*, 2009; Hoff *et al.*, 2007, 2009a, 2009e; Haugeberg *et al.*, 2006; Deodhar *et al.*, 1995]. Patients with positive rheumatoid factor (RF) or antibodies against cyclic citrullinated protein (anti-CCP) have also been found to be at a higher risk of losing hand bone [Boyesen *et al.*, 2009; Haugeberg *et al.*, 2006; Deodhar *et al.*, 1995].

Studies suggest that DXA-BMD loss takes place only in patients with short disease duration while DXR-BMD loss can be detected during the whole disease process [Hoff *et al.*, 2007, 2009a; Deodhar *et al.*, 1995, 2003]. Degenerative bone changes and increased inflammation in the small joints of the hand in the first years of the disease have been suggested to partially explain this finding [Deodhar *et al.*, 1994]. As DXA measures both trabecular and cortical bone a third explanation could be that the rate of trabecular and cortical bone loss is different in early *versus* late stages of the disease. The fact that the two methods for bone measurements are based on completely different techniques and that the precision of the DXR method [Hoff *et al.*, 2008, 2009b; Jorgensen *et al.*, 2000] is better than the DXA method [Haugeberg *et al.*, 2007; Daragon *et al.*, 2001; Alenfeld *et al.*, 2000] may also contribute to the explanation. In the few previous studies which have compared hand DXR and DXA in early RA disease the authors have suggested that changes in DXR are more sensitive than DXA to disease activity [Hoff *et al.*, 2007; Jensen *et al.*, 2004, 2005].

Cross-sectional studies have also demonstrated that hand BMD is lower in RA patients with high disease activity both for DXR [Bottcher *et al.*, 2005a] and DXA [Devlin *et al.*, 1996].

Hand bone loss as response measure to treatment

Suppressing the inflammation by anti-TNF therapy has significantly reduced the progression of radiographic joint damage in RA patients compared with conventional disease-modifying antirheumatic drugs (DMARDs) treatment, e. g. methotrexate [van der Heijde *et al.*, 2006; Breedveld *et al.*, 2006; Keystone *et al.*, 2004; Klareskog *et al.*, 2004; St Clair *et al.*, 2004; Lipsky *et al.*, 2000]. The hypothesis that erosions and hand bone loss are caused by the

same mechanism suggest that anti-inflammatory treatment should have an effect on osteoporosis as well. Two studies have suggested that anti-TNF therapy did not have a significant effect on hand bone loss, but did reduce the bone loss in the hip [Haugeberg *et al.*, 2009; Vis *et al.*, 2006] and spine [Vis *et al.*, 2006]. However, other studies involving more patients showed that patients treated with potent anti-inflammatory treatment such as prednisolone or anti-TNF therapy lost significantly less cortical bone as assessed by DXR compared with treatment with placebo or conventional DMARDs [Hoff *et al.*, 2009e; Guler-Yuksel *et al.*, 2009; Haugeberg *et al.*, 2005]. The fact that patients using prednisolone had a lower rate of cortical hand bone loss than patients using placebo suggest that the potent anti-inflammatory effect of prednisolone exceeded its negative effect on bone in RA patients [Guler-Yuksel *et al.*, 2009; Haugeberg *et al.*, 2005].

The hypothesis of a common cellular mechanism of erosions and periarticular osteoporosis by the osteoclast is further supported by the observation from two treatment studies where the order of hand bone loss and radiographic progression in RA was similar across the different treatment arms [Hoff *et al.*, 2009c; Guler-Yuksel *et al.*, 2009]. Recent results from a study of the RANKL inhibitor denosumab further support the important role of the osteoclast, since this drug inhibited erosions and hand DXA-BMD loss, but not cartilage destruction or inflammation [Cohen *et al.*, 2008; Deodhar *et al.*, 2008]. In addition, anti-TNF therapy has been found to decrease hand bone loss independent of disease activity, supporting the hypothesis that TNF has a direct influence on the osteoclast [Hoff *et al.*, 2009d].

Hand bone loss and radiographic damage

Despite the fact that periarticular osteoporosis and erosions are known as radiographic hallmarks of RA [Arnett *et al.*, 1988], there is a lack of data on the relationship between hand bone loss and radiographic damage. Studies with conventional radiographs have in early studies supported the idea that bone loss precedes the development of erosions [Brook and Corbett, 1977; Bywaters, 1960]. Two cross-sectional studies have revealed a significant correlation (r) of 0.24–0.69 between DXA-BMD and radiographic damage [Ardicoglu *et al.*, 2001; Deodhar *et al.*, 1994], whereas no correlation was seen in a third study [Harrison *et al.*, 2002]. Four longitudinal studies have been performed examining radiographic changes and DXA changes. Two studies revealed no significant correlation [Deodhar *et al.*, 2003; Daragon *et al.*, 2001], while in a 2-year longitudinal study including 43 patients a significant correlation ($r = -0.55$) was found [Berglin *et al.*, 2003]. The fourth study reported that the number of RA patients with early disease losing hand DXA-BMD, defined by the smallest detectable change (SDC) at 24 weeks, was significantly higher than the number of patients with a significant increase in radiographic damage detected by the van der Heijde (vdH) Sharp score at 48 weeks [Haugeberg *et al.*, 2007]. The authors concluded that DXA-BMD was a more sensible method to detect bone damage in patients with early RA than conventional hand radiographic scores.

For the DXR-method, several cross-sectional studies have found DXR-BMD to be lower in patients with high radiographic joint damage scores than in patients with a low radiographic damage score [Jawaid *et al.*, 2006; Bottcher *et al.*, 2004, 2005a, 2005b, 2006a, 2006b, 2006c; Haugeberg *et al.*, 2004]. In all these studies the correlation coefficient (r) between radiographic damage and DXR-BMD ranged from −0.42 to −0.66. Two longitudinal studies have examined the value of hand bone loss as a predictor of radiographic damage. One longitudinal pilot study including 24 patients indicated that DXR-BMD loss in the first year of follow-up in early RA (<1 year disease duration at inclusion) could predict the new development of erosions at 4-year follow-up [Stewart *et al.*, 2004]. Another study including 136 patients confirmed the predictive value of DXR-BMD. In this study DXR-BMD loss in the first year of follow up was an independent predictor for subsequent radiographic damage at 5 and 10 years, even when adjusted for other known predictors of radiographic progression such as baseline radiographic damage, anti-CCP and markers of inflammation [Hoff *et al.*, 2009c].

Conclusion

Quantitative hand bone measurements performed by DXA and DXR have both shown promise as tools to detect early inflammatory bone involvement in RA. Hand bone loss is associated with markers of disease activity [e. g. CRP, erythrocyte sedimentation rate (ESR)] and disease severity (anti-CCP). Furthermore, the magnitude of hand bone loss in RA patients has been found to

be greater than in patients with other inflammatory joint disorders, e. g. psoriatic arthritis. Finally, early hand bone loss is a predictor of subsequent radiographic damage, independent of other predictors for radiographic damage, e. g. anti-CCP and the presence of erosions. Despite the promising results of quantitative bone measures reported in the literature, there is still a need for further studies validating these methods before they may be used routinely in daily clinical care as outcome measures.

Conflict of interest statement

None declared

References

Alamanos, Y., Voulgari, P.V. and Drosos, A.A (2006) Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 36: 182–188.

Alenfeld, F.E., Diessel, E., Brezger, M., Sieper, J., Felsenberg, D. and Braun, J. (2000) Detailed analyses of periarticular osteoporosis in rheumatoid arthritis. *Osteoporos Int* 11: 400–407.

Ardicoglu, O., Ozgocmen, S., Kamanli, A. and Pekkutucu, I. (2001) Relationship between bone mineral density and radiologic scores of hands in rheumatoid arthritis. *J Clin Densitom* 4: 263–269.

Arnett, F.C., Edworthy, S.M., Bloch, D.A., McShane, D.J., Fries, J.F., Cooper, N.S. *et al.* (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31: 315–324.

Barnett, E. and Nordin, B.E. (1960) The radiological diagnosis of osteoporosis: a new approach. *Clin Radiol* 11: 166–174.

Berglin, E., Lorentzon, R., Nordmark, L., Nilsson-Sojka, B. and Rantapaa, D.S. (2003) Predictors of radiological progression and changes in hand bone density in early rheumatoid arthritis. *Rheumatology (Oxford)* 42: 268–275.

Blake, G.M. and Fogelman, I. (1997) Technical principles of dual energy x-ray absorptiometry. *Semin Nucl Med* 27: 210–228.

Boini, S. and Guillemin, F. (2001) Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. *Ann Rheum Dis* 60: 817–827.

Bottcher, J., Malich, A., Pfeil, A., Petrovitch, A., Lehmann, G., Heyne, J.P. *et al.* (2004) Potential clinical relevance of digital radiogrammetry for quantification of periarticular bone demineralization in patients suffering from rheumatoid arthritis depending on severity and compared with DXA. *Eur Radiol* 14: 631–637.

Bottcher, J., Pfeil, A., Heinrich, B., Lehmann, G., Petrovitch, A., Hansch, A. *et al.* (2005a) Digital radiogrammetry as a new diagnostic tool for estimation of disease-related osteoporosis in rheumatoid arthritis compared with pQCT. *Rheumatol Int* 25: 457–464.

Bottcher, J., Pfeil, A., Mentzel, H., Kramer, A., Schafer, M.L., Lehmann, G. *et al.* (2006a) Peripheral bone status in rheumatoid arthritis evaluated by digital X-ray radiogrammetry and compared with multisite quantitative ultrasound. *Calcif Tissue Int* 78: 25–34.

Bottcher, J., Pfeil, A., Rosholm, A., Petrovitch, A., Seidl, B.E., Malich, A. *et al.* (2005b) Digital X-ray radiogrammetry combined with semiautomated analysis of joint space widths as a new diagnostic approach in rheumatoid arthritis: a cross-sectional and longitudinal study. *Arthritis Rheum* 52: 3850–3859.

Bottcher, J., Pfeil, A., Rosholm, A., Schafer, M.L., Malich, A., Petrovitch, A. *et al.* (2006b) Computerized digital imaging techniques provided by digital X-ray radiogrammetry as new diagnostic tool in rheumatoid arthritis. *J Digit Imaging* 19: 279–288.

Bottcher, J., Pfeil, A., Rosholm, A., Soros, P., Petrovitch, A., Schaefer, M.L. *et al.* (2006c) Computerized quantification of joint space narrowing and periarticular demineralization in patients with rheumatoid arthritis based on digital x-ray radiogrammetry. *Invest Radiol* 41: 36–44.

Boyesen, P., Hoff, M., Odegard, S., Haugeberg, G., Syversen, S.W., Gaarder, P.I. *et al.* (2009) Antibodies to cyclic citrullinated protein and erythrocyte sedimentation rate predict hand bone loss in patients with rheumatoid arthritis of short duration: a longitudinal study. *Arthritis Res Ther* 11: R103.

Breedveld, F.C., Weisman, M.H., Kavanaugh, A.F., Cohen, S.B., Pavelka, K., van Vollenhoven, R. *et al.* (2006) The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 54: 26–37.

Brook, A. and Corbett, M. (1977) Radiographic changes in early rheumatoid disease. *Ann Rheum Dis* 36: 71–73.

Bywaters, E.G. (1960) The early radiological signs of rheumatoid arthritis. *Bull Rheum Dis* 11: 231–234.

Cann, C.E. (1988) Quantitative CT for determination of bone mineral density: a review. *Radiology* 166: 509–522.

Cohen, S.B., Dore, R.K., Lane, N.E., Ory, P.A., Peterfy, C.G., Sharp, J.T. *et al.* (2008) 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* 58: 1299–1309.

Daragon, A., Krzanowska, K., Vittecoq, O., Menard, J.F., Hau, I., Jouen-Beades, F. *et al.* (2001) Prospective X-ray densitometry and ultrasonography study of the hand bones of patients with rheumatoid arthritis of recent onset. *Joint Bone Spine* 68: 34–42.

Deodhar, A.A., Brabyn, J., Jones, P.W., Davis, M.J. and Woolf, A.D. (1994) Measurement of hand bone mineral content by dual energy x-ray absorptiometry: development of the method, and its application in normal volunteers and in patients with rheumatoid arthritis. *Ann Rheum Dis* 53: 685–690.

Deodhar, A.A., Brabyn, J., Jones, P.W., Davis, M.J. and Woolf, A.D. (1995) Longitudinal study of hand bone densitometry in rheumatoid arthritis. *Arthritis Rheum* 38: 1204–1210.

Deodhar, A.A., Brabyn, J., Pande, I., Scott, D.L. and Woolf, A.D. (2003) Hand bone densitometry in rheumatoid arthritis, a five year longitudinal study: an outcome measure and a prognostic marker. *Ann Rheum Dis* 62: 767–770.

Deodhar, A.A., Dore, R.K., Sharp, J., Mandel, D., Schechtman, J., Shergy, W. *et al.* (2008) Increase in hand bone mineral density in patients with rheumatoid arthritis is associated with decreased progression of bone erosions after denosumab therapy. *Ann Rheum Dis* 67(Suppl 2): 128(Abstract).

Devlin, J., Lilley, J., Gough, A., Huissoon, A., Holder, R., Reece, R. *et al.* (1996) Clinical associations of dual-energy X-ray absorptiometry measurement of hand bone mass in rheumatoid arthritis. *Br J Rheumatol* 35: 1256–1262.

Emery, P., Genovese, M.C., van Vollenhoven, R., Sharp, J.T., Patra, K. and Sasso, E.H. (2009) Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J Rheumatol* 36: 1429–1441.

Feldmann, M., Brennan, F.M. and Maini, R.N. (1996) Rheumatoid arthritis. *Cell* 85: 307–310.

Garnero, P., Tabassi, N.C. and Voorzanger-Rousselot, N. (2008) Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with etanercept. *J Rheumatol* 35: 2313–2315.

Goldring, S.R. and Gravallese, E.M. (2004) Bisphosphonates: environmental protection for the joint? *Arthritis Rheum* 50: 2044–2047.

Gravallese, E.M. (2002) Bone destruction in arthritis. *Ann Rheum Dis* 61(Suppl 2): ii84–ii86.

Gravallese, E.M., Harada, Y., Wang, J.T., Gorn, A.H., Thornhill, T.S. and Goldring, S.R. (1998) Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *Am J Pathol* 152: 943–951.

Green, M.J. and Deodhar, A.A. (2001) Bone changes in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 15: 105–123.

Guler-Yuksel, M., Allaart, C.F., Goekoop-Ruiterman, Y.P., de Vries-Bouwstra, J.K., van Groenendael, J.H., Mallee, C. *et al.* (2009) Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 68: 330–336.

Harrison, B.J., Hutchinson, C.E., Adams, J., Bruce, I.N. and Herrick, A.L. (2002) Assessing periarticular bone mineral density in patients with early psoriatic arthritis or rheumatoid arthritis. *Ann Rheum Dis* 61: 1007–1011.

Haugeberg, G., Green, M.J., Conaghan, P.G., Quinn, M., Wakefield, R., Proudman, S.M. *et al.* (2007) Hand bone densitometry: a more sensitive standard for the assessment of early bone damage in rheumatoid arthritis. *Ann Rheum Dis* 66: 1513–1517.

Haugeberg, G., Conaghan, P.G., Quinn, M. and Emery, P. (2009) Bone loss in active early rheumatoid arthritis patients treated with infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a twelve-month randomized, double blind, placebo-controlled study. *Ann Rheum Dis* 68: 1898–1901.

Haugeberg, G., Green, M.J., Quinn, M.A., Marzo-Ortega, H., Proudman, S., Karim, Z. *et al.* (2006) Hand bone loss in early undifferentiated arthritis: evaluating bone mineral density loss before the development of rheumatoid arthritis. *Ann Rheum Dis* 65: 736–740.

Haugeberg, G., Lodder, M.C., Lems, W.F., Uhlig, T., Orstavik, R.E., Dijkmans, B.A. *et al.* (2004) Hand cortical bone mass and its associations with radiographic joint damage and fractures in 50–70 year old female patients with rheumatoid arthritis: cross sectional Oslo-Truro-Amsterdam (OSTRA) collaborative study. *Ann Rheum Dis* 63: 1331–1334.

Haugeberg, G., Strand, A., Kvien, T.K. and Kirwan, J.R. (2005) Reduced loss of hand bone density with prednisolone in early rheumatoid arthritis: results from a randomized placebo-controlled trial. *Arch Intern Med* 165: 1293–1297.

Haugeberg, G., Uhlig, T., Falch, J.A., Halse, J.I. and Kvien, T.K. (2000a) Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum* 43: 522–530.

Haugeberg, G., Uhlig, T., Falch, J.A., Halse, J.I. and Kvien, T.K. (2000b) 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* 43: 2776–2784.

Herrak, P., Gortz, B., Hayer, S., Redlich, K., Reiter, E., Gasser, J. *et al.* (2004) Zoledronic acid protects against local and systemic bone loss in tumor necrosis factor-mediated arthritis. *Arthritis Rheum* 50: 2327–2337.

Hoff, M., Bøyesen, P., Haugeberg, G., Vis, M., Haavardsholm, E.A., Uhlig, T. *et al.* (2009a) High disease activity is a predictor of subsequent 5-year

cortical hand bone loss in patients with longstanding rheumatoid arthritis. The Oslo, Truro and Amsterdam (OSTRA) collaborative study. *Ann Rheum Dis* 68(Suppl 3): 166(Abstract).

Hoff, M., Dhainaut, A., Kvien, T.K., Forslind, K., Kalvesten, J. and Haugeberg, G. (2009b) Short-time in vitro and in vivo precision of direct digital X-ray radiogrammetry. *J Clin Densitom* 12: 17–21.

Hoff, M., Dhainaut, A., Kvien, T.K. and Haugeberg, G. (2008) Short time precision assessed with digital X-ray radiogrammetry in healthy individuals and rheumatoid arthritis patients. *Ann Rheum Dis* 67(Suppl 2): 563(Abstract).

Hoff, M., Haugeberg, G. and Kvien, T.K. (2007) Hand bone loss as an outcome measure in established rheumatoid arthritis: 2-year observational study comparing cortical and total bone loss. *Arthritis Res Ther* 9: R81.

Hoff, M., Haugeberg, G., Odegard, S., Syversen, S., Landewe, R., van der Heide, D. and Kvien, T.K. (2009c) Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. *Ann Rheum Dis* 68: 324–329.

Hoff, M., Kvien, T.K., Elden, A., Kalvesten, J., Kavanaugh, A.F. and Haugeberg, G. (2009d) Adalimumab reduces hand bone loss in rheumatoid arthritis independent of clinical response: Subanalysis of the PREMIER study. *Ann Rheum Dis* 68(Suppl 3): 452(Abstract).

Hoff, M., Kvien, T.K., Kalvesten, J., Elden, A. and Haugeberg, G. (2009e) Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. *Ann Rheum Dis* 68: 1171–1176.

Huusko, T.M., Korpela, M., Karppi, P., Avikainen, V., Kautiainen, H. and Sulkava, R. (2001) Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland. *Ann Rheum Dis* 60: 521–522.

Hyldstrup, L. and Nielsen, S.P. (2001) Metacarpal index by digital X-ray radiogrammetry: normative reference values and comparison with dual X-ray absorptiometry. *J Clin Densitom* 4: 299–306.

Jarrett, S.J., Conaghan, P.G., Sloan, V.S., Papanastasiou, P., Ortmann, C.E., O'Connor, P.J. *et al.* (2006) Preliminary evidence for a structural benefit of the new bisphosphonate zoledronic acid in early rheumatoid arthritis. *Arthritis Rheum* 54: 1410–1414.

Jawaid, W.B., Crosbie, D., Shotton, J., Reid, D.M. and Stewart, A. (2006) Use of digital X ray radiogrammetry in the assessment of joint damage in rheumatoid arthritis. *Ann Rheum Dis* 65: 459–464.

Jensen, T., Hansen, M., Jensen, K.E., Podenphant, J., Hansen, T.M. and Hyldstrup, L. (2005) Comparison of dual X-ray absorptiometry (DXA), digital X-ray radiogrammetry (DXR), and conventional radiographs in the evaluation of osteoporosis and bone erosions in patients with rheumatoid arthritis. *Scand J Rheumatol* 34: 27–33.

Jensen, T., Klarlund, M., Hansen, M., Jensen, K.E., Podenphant, J., Hansen, T.M. *et al.* (2004) Bone loss in unclassified polyarthritis and early rheumatoid arthritis is better detected by digital X ray radiogrammetry than dual X ray absorptiometry: relationship with disease activity and radiographic outcome. *Ann Rheum Dis* 63: 15–22.

Jergas, M., Uffmann, M., Escher, H., Gluer, C.C., Young, K.C., Grampp, S. *et al.* (1994) Interobserver variation in the detection of osteopenia by radiography and comparison with dual X-ray absorptiometry of the lumbar spine. *Skeletal Radiol* 23: 195–199.

Jorgensen, J.T., Andersen, P.B., Rosholm, A. and Bjarnason, N.H. (2000) Digital X-ray radiogrammetry: a new appendicular bone densitometric method with high precision. *Clin Physiol* 20: 330–335.

Kanis, J.A., Burlet, N., Cooper, C., Delmas, P.D., Reginster, J.Y., Borgstrom, F. *et al.* (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 19: 399–428.

Keystone, E.C., Kavanaugh, A.F., Sharp, J.T., Tannenbaum, H., Hua, Y., Teoh, L.S. *et al.* (2004) Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 50: 1400–1411.

Klareskog, L., Catrina, A.I. and Paget, S. (2009) Rheumatoid arthritis. *Lancet* 373(9664): 659–672.

Klareskog, L., van der Heijde, D., de Jager, J.P., Gough, A., Kalden, J., Malaise, M. *et al.* (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363(9410): 675–681.

Kvien, T.K., Glennas, A., Knudsrod, O.G., Smedstad, L.M., Mowinckel, P. and Forre, O. (1997) The prevalence and severity of rheumatoid arthritis in Oslo. Results from a county register and a population survey. *Scand J Rheumatol* 26: 412–418.

Lam, J., Takeshita, S., Barker, J.E., Kanagawa, O., Ross, F.P. and Teitelbaum, S.L. (2000) TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 106: 1481–1488.

Lipsky, P.E., van der Heijde, D., St Clair, E.W., Furst, D.E., Breedveld, F.C., Kalden, J.R. *et al.* (2000) Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 343: 1594–1602.

Murphy, E., Bresnihan, B. and FitzGerald, O. (2008) Measurement of periarticular bone mineral density in the hands of patients with early inflammatory arthritis

using dual energy X-ray absorptiometry. *Clin Rheumatol* 27: 763–766.

Nielsen, S.P. (2001) The metacarpal index revisited: a brief overview. *J Clin Densitom* 4: 199–207.

Njeh, C.F., Boivin, C.M. and Langton, C.M. (1997) The role of ultrasound in the assessment of osteoporosis: a review. *Osteoporos Int* 7: 7–22.

Njeh, C.F. and Genant, H.K. (2000) Bone loss.Quantitative imaging techniques for assessing bone mass in rheumatoid arthritis. *Arthritis Res* 2: 446–450.

Orstavik, R.E., Haugeberg, G., Mowinckel, P., Hoiseth, A., Uhlig, T., Falch, J.A. *et al.* (2004a) Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. *Arch Intern Med* 164: 420–425.

Orstavik, R.E., Haugeberg, G., Uhlig, T., Mowinckel, P., Falch, J.A., Halse, J.I. *et al.* (2004b) Self reported non-vertebral fractures in rheumatoid arthritis and population based controls: incidence and relationship with bone mineral density and clinical variables. *Ann Rheum Dis* 63: 177–182.

Pettit, A.R., Ji, H., von Stechow, D., Muller, R., Goldring, S.R., Choi, Y. *et al.* (2001) TRANCE/RANKL knockout mice are protected from bone erosion in a serum transfer model of arthritis. *Am J Pathol* 159: 1689–1699.

Redlich, K., Hayer, S., Ricci, R., David, J.P., Tohidast-Akrad, M., Kollias, G. *et al.* (2002) Osteoclasts are essential for TNF-alpha-mediated joint destruction. *J Clin Invest* 110: 1419–1427.

Rosholm, A., Hyldstrup, L., Backsgaard, L., Grunkin, M. and Thodberg, H.H. (2001) Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. *Osteoporos Int* 12: 961–969.

Sambrook, P.N. (2000) The skeleton in rheumatoid arthritis: common mechanisms for bone erosion and osteoporosis? *J Rheumatol* 27: 2541–2542.

Schett, G. (2007) Cells of the synovium in rheumatoid arthritis. Osteoclasts. *Arthritis Res Ther* 9: 203.

Schett, G. (2009) Osteoimmunology in rheumatic diseases. *Arthritis Res Ther* 11: 210.

Schett, G., Hayer, S., Zwerina, J., Redlich, K. and Smolen, J.S. (2005) Mechanisms of disease: the link between RANKL and arthritic bone disease. *Nat Clin Pract Rheumatol* 1: 47–54.

Schett, G., Zwerina, J. and David, J.P. (2008) The role of Wnt proteins in arthritis. *Nat Clin Pract Rheumatol* 4: 473–480.

Sims, N.A., Green, J.R., Glatt, M., Schlict, S., Martin, T.J., Gillespie, M.T. *et al.* (2004) Targeting osteoclasts with zoledronic acid prevents bone destruction in collagen-induced arthritis. *Arthritis Rheum* 50: 2338–2346.

Smolen, J.S., Aletaha, D., Koeller, M., Weisman, M.H. and Emery, P. (2007) New therapies for treatment of rheumatoid arthritis. *Lancet* 370(9602): 1861–1874.

Smolen, J.S., Han, C., van der Heijde, D., Emery, P., Bathon, J.M., Keystone, E. *et al.* (2009) Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 68: 823–827.

St Clair, E.W., van der Heijde, D., Smolen, J.S., Maini, R.N., Bathon, J.M., Emery, P. *et al.* (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 50: 3432–3443.

Stewart, A., Mackenzie, L.M., Black, A.J. and Reid, D.M. (2004) Predicting erosive disease in rheumatoid arthritis. A longitudinal study of changes in bone density using digital X-ray radiogrammetry: a pilot study. *Rheumatology (Oxford)* 43: 1561–1564.

Uhlig, T., Kvien, T.K., Glennas, A., Smedstad, L.M. and Forre, O. (1998) The incidence and severity of rheumatoid arthritis, results from a county register in Oslo, Norway. *J Rheumatol* 25: 1078–1084.

van der Heijde, D. (1996) Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. *Baillieres Clin Rheumatol* 10: 435–453.

van der Heijde, D. (2001) Radiographic progression in rheumatoid arthritis: does it reflect outcome? Does it reflect treatment? *Ann Rheum Dis* 60(Suppl 3): iii47–iii50.

van der Heijde, D., Klareskog, L., Rodriguez-Valverde, V., Codreanu, C., Bolosiu, H., Melo-Gomes, J. *et al.* (2006) Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 54: 1063–1074.

van Staa, T.P., Geusens, P., Bijlsma, J.W., Leufkens, H.G. and Cooper, C. (2006) Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 54: 3104–3112.

Vis, M., Havaardsholm, E.A., Haugeberg, G., Uhlig, T., Voskuyl, A.E., van de Stadt, R.J. *et al.* (2006) 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* 65: 1495–1499.

Young, A. and Koduri, G. (2007) Extra-articular manifestations and complications of rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 21: 907–927.