Editorial

Measuring metacarpal cortical bone by digital x-ray radiogrammetry: a step forward?

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Published: 1 October 2009
This article is online at http://arthritis-research.com/content/11/5/127

Arthritis Research & Therapy 2009, **11**:127 (doi:10.1186/ar2788)

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Abstract

Changes in metacarpal cortical bone mineral density (BMD) using digital x-ray radiogrammetry were studied in patients with early rheumatoid arthritis. After 1, 2, and 5 years, large BMD losses were found: −1.7%, −2.8%, and −5.6%, respectively. Elevated erythrocyte sedimentation rate and anti-cyclic citrullinated peptide levels were independent predictors of bone loss, indicating that the largest amount of bone loss was found in patients with severe inflammation and high production of auto-antibodies, who are known to be at the highest risk of developing radiological bone damage. Studies are needed about the spatial and time relationship between erosions and juxta-articular and metacarpal bone loss.

The elegant study by Bøyesen and colleagues [1] in the previous issue of *Arthritis Research & Therapy*, in which they observed the changes in hand bone mineral density (BMD) using digital x-ray radiogrammetry (DXR) in 163 patients with early rheumatoid arthritis (RA), is most welcome. DXR measures the cortical thickness, width, and porosity of the central parts of metacarpals 2 to 4. After 1, 2, and 5 years of observation, the decreases in hand BMD were −1.7%, −2.8%, and −5.6%, respectively. Elevated levels of both erythrocyte sedimentation rate (ESR) and anti-cyclic citrullinated peptide (anti-CCP) were independent predictors of hand bone loss at all time points, indicating that the largest amounts of bone loss were found in patients with severe inflammation and high levels of auto-antibodies; from earlier data, we know that these patients are prone to develop severe RA with radiological joint damage [2].

RA is a chronic progressive disorder characterised by synovitis, bone and cartilage degradation of the joints, and extra-articular symptoms. Based on the dramatic improvement in treatment options in RA, clinical remission is a realistic target of therapy [2]. In particular, the use of biologicals early in the course of RA is exciting and addresses two of the most important research questions in modern rheumatology: is it possible to predict which RA patients will have a favourable response to conventional (methotrexate, or MTX) therapy? And what are the characteristics of RA patients with an unfavourable prognosis, estimated by radiological joint damage, for which more aggressive therapy is indicated?

Thus, there is an urgent need to develop validated assessment tools for identifying patients who are at risk for a poor prognosis, estimated by early radiological joint damage. Juxta-articular bone loss and subchondral bone oedema due to the replacement of marrow fat by heavily vascularised inflammatory cells are the earliest signs of bone involvement in RA and may even precede the development of radiologically detectable erosions of the joint [3,4].

In the Norwegian study, changes in hip and spine BMD were not mentioned, but in the BeST (Behandel Strategieën) study (also in patients with early RA), it was observed that the hand bone loss was roughly two to five times higher than the generalised bone loss at the spine and hips [5]. This difference presumably reflects the fact that BMD changes at the hands are more sensitive to cytokine stimulation in the adjacent inflamed joints. Güler-Yüksel and colleagues [5] observed that the changes in hand BMD mirror the progression of radiological joint damage according to the Sharp-van der Heijde score (SHS). This inverse relationship

anti-CCP = anti-cyclic citrullinated peptide; BMD = bone mineral density; DXR = digital x-ray radiogrammetry; ESR = erythrocyte sedimentation rate; IL = interleukin; MTX = methotrexate; RA = rheumatoid arthritis; RANKL = receptor activator of nuclear factor-kappa B ligand; SHS = Sharp-van der Heijde score.

suggests that adjacent joint damage and cortical metacarpal bone loss presumably result from the same mechanisms: inflammation-driven upregulation of tumour necrosis factor-alpha, interleukin-1 (IL-1), IL-6, and receptor activator of nuclear factor-kappa B ligand (RANKL), leading to stimulation of osteoclastic bone resorption, in combination with inhibited osteoblastic bone formation, at least partly related to the upregulation of dickkopf-1 [6]. If indeed the mechanisms are similar, does aggressive antirheumatic therapy protect against both local joint damage and cortical metacarpal bone loss? The answer is yes, as shown for combination therapy of MTX with adalimumab, for combination therapy with MTX and prednisone or infliximab, and for denosumab [7-9].

One limitation of the study is the lack of data on clinical joint inflammation and radiographic joint damage (SHS) for determining the correlation in space and time with cortical metacarpal bone loss. Indeed, periarticular trabecular bone loss, cortical bone loss (which is most pronounced at the endocortical site), and subchondral bone oedema are probably the first detectable signs of subchondral inflammation. This could be explained by direct communication between the joints and bone marrow by upregulated local blood flow or by the presence of radiologically still-undetectable small erosions or by both [2,3]. Unfortunately, DXR does not allow us to specify the degree to which bone loss occurs at the endocortical bone site and at the periosteal site. The tight relationship between SHS and hand bone loss has another consequence: it could be argued that the SHS at baseline is missing in the Norwegian prediction model. Another limitation is the lack of data on bone markers, such as the RANKL/osteoprotegerin ratio and bone and cartilage markers (CTX-1 and -2), which independently predict radiographic joint damage in RA [10,11].

The main disadvantage of the SHS is that it is a time-consuming and difficult scoring method, usually performed only in clinical trials. The use of hand DXR is potentially attractive since the measurements can be performed with standard x-rays of the hands and because of the early finding of local hand bone loss. On the other hand, the devices to measure the metacarpals are not widely available, and sending the digital radiographs to a central laboratory may be costly. Second, a crucial question remains: what is the clinical relevance of measuring local hand bone density? However, the results of the Norwegian study should incite researchers to further analyse the sequence of juxta-articular bone events (bone oedema and periarticular trabecular and cortical bone loss and erosions) in early RA.

In summary, the observation that elevated levels of both ESR and anti-CCP are predictors of hand bone loss measured by DXR seems to be adequate and important. Nevertheless, more data and clinical experience are needed before the use of hand DXR can be successfully introduced in daily practice.

Competing interests

The authors declare that they have no competing interests.

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