

## Editorial

# Diagnosis of periarticular osteoporosis in rheumatoid arthritis using digital X-ray radiogrammetry

Joachim Böttcher and Alexander Pfeil

Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller-University Jena, Erlanger Allee, 07747 Jena, Germany

Corresponding author: Joachim Böttcher, [joachim.boettcher@med.uni-jena.de](mailto:joachim.boettcher@med.uni-jena.de)

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## Abstract

Osteoporosis can manifest in two ways in rheumatoid arthritis: generalized bone loss, which may result from immobility, the inflammatory process *per se* and/or treatments such as steroids; and periarticular demineralization, which is probably due to local release of inflammatory agents. Digital X-ray radiogrammetry (DXR) is an effective and sensitive modality for monitoring periarticular osteoporosis, which is among the earliest features of rheumatoid arthritis, preceding bone erosions. DXR is a promising technique, which can provide quantitative data that allow early diagnosis. During the course of rheumatoid arthritis it can be deployed in combination with established X-ray scoring methods to inform decisions regarding the optimal therapy to prevent joint destruction.

RA is a systemic inflammatory disease; in 80% of patients the small joints of the hand are affected, leading to destruction of periarticular tissue. The characteristic pattern of juxta-articular inflammatory involvement includes cartilage destruction, periarticular osteoporosis and bone erosion [2].

Many studies have revealed the influence of various cytokines on dysregulation of bone and cartilage remodelling. Recently, receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) and osteoprotegerin (a decoy receptor for RANKL) were identified as central regulators of osteoclast recruitment and activation.

## Introduction

In a well documented and extensive study of peripheral bone loss in established rheumatoid arthritis (RA), Hoff and colleagues [1] evaluated bone loss in the hand using digital X-ray radiogrammetry (DXR) and dual energy X-ray absorptiometry (DXA). They compared peripheral demineralization with central bone loss (quantified by axial DXA measurements) at the lumbar spine and femoral neck, considering disease duration over an observation period of 2 years.

This carefully conducted study revealed significant peripheral hand bone loss (estimated by DXR), independent of disease duration. Whole-hand bone mineral density, determined using DXA (DXA-BMD), indicated demineralization only during the first 3 years of RA. The study also highlighted that disease activity independently predicted decline in DXR-BMD, but the loss of hand DXA-BMD was similar in patients with high disease activity and in those with low disease activity. These findings indicate that DXR surpassed DXA as an outcome measure in both early and late stages of RA.

Osteoporosis is an early and common feature in RA and occurs in two forms during the course of the disease [2,3]: periarticular osteopenia in close proximity to inflamed joints, which is a typical phenomenon in early and prolonged rheumatoid disease; and generalized osteoporosis, which affects the axial and appendicular bones. Inflammation has the effect of provoking more severe and accelerated bone loss in the hand as compared with hip and spine [1]. Because periarticular osteoporosis in RA is also the first disease-related morphological sign before erosions and joint space narrowing occur, it has been proposed that quantitative hand bone estimates that identify periarticular osteoporosis be used as outcome measures in RA [1,4].

Therefore, various osteodensitometric techniques have been developed that focus on quantification of RA-related bone loss. Nevertheless, early detection of periarticular demineralization remained unsatisfactory without the use of special computer-aided diagnosis (CAD) solutions. One of the most challenging applications of CAD appears to be in exploiting

CAD = computer-aided diagnosis; DXA = dual energy X-ray absorptiometry; DXR = digital X-ray radiogrammetry; MCI = metacarpal index; RA = rheumatoid arthritis; RANKL = receptor activator of nuclear factor- $\kappa$ B ligand.

the potential of DXR to estimate and quantify cortical bone status using digitized radiographs [5,6].

### Clinical applications of DXR

DXR is a new operator-independent diagnostic tool that provides automated measurements of cortical BMD and of metacarpal index (MCI), based on estimates of cortical thickness using digitized radiographs. The computer algorithms employed in the DXR technique automatically define regions of interest around the narrowest parts of the second, third and fourth metacarpals, and they then identify the outer and inner cortical edges of the cortical bone parts examined. The mean of the cortical thickness and overall bone cortical thickness of the second, third and fourth metacarpals are estimated. Subsequently, the cortical volume per area is calculated for each bone.

This CAD technique exhibits excellent intra-radiograph (0.05% to 0.33%) and inter-radiograph (0.26% to 1.54%) reproducibility [5], providing confidence that estimated demineralization is in fact disease related and not based on precision error of the densitometric method itself. The influence of RA-related bony defects and erosions on DXR calculations can be minimized because measurements are made at the diaphyseal part of the metacarpal bones [5,6].

### DXR in rheumatoid arthritis

Patients with RA often exhibit an accelerated course of progression during the early years of disease, and therefore it has been recommended that conventional imaging of the hands and feet be done every year during the initial period after RA onset. Various scoring methods have been validated and established that are based on conventional radiography, the 'gold standard', and allow evaluation of RA progression. X-ray scoring methods are designed to allow semiquantitative measurement of radiographically visible disease-related alterations, in particular erosions and joint space narrowing caused by cartilage damage. However, metacarpal osteopenia predates periarticular erosions and joint destruction [2-4,7]. Apart from these techniques, it is only possible to determine the extent of periarticular demineralization by visual assessment, which is inadequate.

Recently, Stewart and coworkers [7] verified that DXR, used to quantify RA-related osteoporosis, predicted well the erosive status of patients. In this study the reduction in DXR-BMD after 1 year was rather specific (100%) and highly sensitive (63%) in identifying those patients with an accelerated course of RA, with development of erosions after a 4-year period of observation. In addition, DXR-BMD was independently associated with radiographic hand joint damage [8].

A possible limitation of DXR may be that it allows measurement of BMD only in the cortical partition; this is because of the minor bone metabolism of cortical bone matrix compared with trabecular bone tissue. Otherwise, cortical thinning of

periarticular bone, enhanced by the inflammatory process, is a typical feature of bone destruction in RA [3], which can occur as a result of high bone turnover on the inner bone surface.

Hoff and colleagues [1] reported that patients with high disease activity, as indicated by DXR but not DXA, exhibit advanced hand demineralization; this was corroborated by further comparative studies [8-10].

In comparison with other osteodensitometric techniques (DXA, peripheral quantitative computed tomography and quantitative ultrasound) [1,9,10], DXR identifies and quantifies RA-related cortical bone loss more reliably, taking into account disease activity and severity of RA. In addition, DXR offers an opportunity to analyze all available hand radiographs both prospectively and retrospectively throughout the course of RA.

In a longitudinal study of patients with early RA [6], DXR parameters identified an accentuated relative decrease of up to 14.3% in BMD during the first year of clinical RA manifestations. After a disease duration of more than 1 year, a flatter but persistent decline in DXR-BMD and DXR-MCI was observed, corroborating the findings reported by Hoff and colleagues [1]. This study identified an average annual bone loss of 3.6% and an average annual reduction in DXR-MCI of 3.2% during the 6-year period of follow up [6].

### Conclusion

DXR as a CAD tool provides quantitative data about periarticular RA-related osteoporosis and serves as a promising supplement to the X-ray scoring methods, allowing earlier diagnosis of RA, which is essential for optimal and timely treatment. Further prospective studies should focus on comparison with established X-ray scoring methods to validate the DXR method, on the potential of DXR to evaluate the therapeutic effects of both newly developed and established treatment strategies, and on the determination of cut-off values for DXR parameters to differentiate patients with (very) early RA from those with transient nonspecific joint disorders.

### Competing interests

The authors declare that they have no competing interests.

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