**High-resolution imaging of bone and joint architecture in rheumatoid arthritis**

Paccou Julien, Edwards Mark Hiley, Moss Charlotte, Dennison Elaine, Cooper Cyrus

Affiliations:

MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD

Corresponding author:

Cyrus Cooper, M.D., Ph.D.

MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD

Tel: +44 (0)23 8077 7624

Keywords: Rheumatoid arthritis, fracture, bone turnover markers, High resolution peripheral quantitative computed tomography, volumetric bone mineral density, microarchitecture and bone erosions.

Short title of paper: HR-pQCT in patients with RA

Word count: 4080

Number of tables and figures: 4

Conflict of interest statement: Professor Cooper has received consultancy fees/honoraria from Servier, Eli Lilly, Merck, Amgen, Alliance, Novartis, Medtronic, GSK, and Roche.

**Abstract**

Introduction: Rheumatoid Arthritis (RA) is characterised by local and systemic bone loss caused by increased bone resorption. We describe the current utilisation of high-resolution peripheral quantitative computed tomography (HR-pQCT) in the evaluation of bone and joint in RA.

Sources of data: PubMed was searched for publications using keywords that included “bone microarchitecture”, “high resolution peripheral quantitative computed tomography”, and “rheumatoid arthritis”.

Areas of agreement: HR-pQCT may simultaneously allow assessment of trabecular and cortical bone parameters and be a useful method for depicting bone erosions.

Areas of controversy: HRpQCT only assesses bone microarchitecture at the distal radius and tibia. Controversy exists regarding the optimal way to differentiate cortical and trabecular regions.

Growing points: Although HR-pQCT is currently a research tool, there is potential for its use in the clinical diagnosis and management in RA.

Further research is required to evaluate the clinical relevance of imaging abnormalities identified in RA patients

**Introduction**

Rheumatoid arthritis (RA) is characterized by an inflammatory process which targets both the joints and bone. RA is considered as an independent risk factor in the aetiology of secondary osteoporosis which is reflected by its inclusion into the fracture risk assessment tool (FRAX®) **(1)**. The overall prevalence of osteoporosis in RA is in the order of 20-30% at the spine and 7-26% at the hip **(2)**. Currently, dual energy X-ray absorptiometry (DXA) is used clinically to monitor areal bone mineral density (aBMD) in RA **(3)**. However, standard DXA does not provide information on bone microarchitecture. The development of high-resolution peripheral quantitative computed tomography (HR-pQCT) has enabled us to investigate bone in greater detail **(4)**. Specifically, this evolving technique offers new possibilities to explore bone geometry, density and microstructure in patients with RA. Here we describe the current utilisation of HR‑pQCT in the evaluation of bone and joint in patients with RA using a systematic review of the literature.

**Rheumatoid arthritis and fracture**

Patients with RA are at increased risk of suffering osteoporotic fractures **(5-7)**. A large, population-based cohort study was performed by Van Staa and colleagues to assess the risk of fracture in patients with RA using the British General Practice Research Database (GPRD) **(5)**. There were 30,262 patients with RA (≥40 years), of whom 2,460 experienced a fracture during follow-up (median of 7.6 years). Patients with RA, compared with controls, had an increased risk of fracture (adjusted RR for clinical osteoporotic fractures 1.5, 95% confidence interval [95% CI] 1.4–1.6) most marked at the hip (RR 2.0, 95% CI 1.8–2.3) and spine (RR 2.4, 95% CI 2.0–2.8). Moreover, patients with longstanding RA (>10 years’ duration), a low body mass index (BMI) and those who used oral glucocorticoids (GCs) had a higher risk of hip fracture **(5)**. In a Southampton case–control study the risk of hip fracture in patients with RA and those taking GCs was investigated. Three hundred consecutive patients with RA (>50 years) were compared with 600 controls. The effects of RA and GCs were found to be largely independent of one another and interestingly, patients with RA who were not receiving GCs doubled their risk of suffering a hip fracture even if this risk was most closely associated with functional impairment **(6)**. Another large, population-based cohort study has confirmed these results **(7)**. During a median 1.63-year follow-up, 872 (1.9%) of 47,034 RA patients experienced a fracture. After adjustment for confounders, an increase in the risk of fracture was found (HR 1.26, 95% CI 1.15-1.38) and was most marked at the hip (HR 1.44, 95% CI 1.24-1.67). Moreover, prior use of GCs also increased risk of osteoporotic fracture (HR 1.36, 95% CI 0.86-2.14) **(7)**. Furthermore, RA patients also have a higher prevalence of asymptomatic vertebral fractures and incidence of vertebral fracture **(8, 9)**. Clearly, this highlights the importance of specific assessment of these events, for example with vertebral fracture assessment at the time of DXA.

Individuals with RA are evidently at greater risk of fracture, particularly of the hip. There are several factors shown to augment the likelihood, including longer disease duration and use of GCs. Part of the increased risk would be expected to occur through an increased rate of falling although there is also a direct effect on bone health.

**Rheumatoid arthritis and bone strength**

Bone strength is determined by bone density and bone quality (bone remodeling, microarchitectural organization of the bone, collagen composition and degree of mineralization of bone matrix).

Bone mineral density by DXA

Several studies have shown a lower BMD in patients with RA as compared to controls. The overall prevalence of osteoporosis in RA is in the order of 20-30% at the spine and 7-26% at the hip **(2)**. In a cohort of 148 patients with early RA (compared to 730 normal controls), BMD was assessed by DXA before treatment with GCs or disease-modifying anti-rheumatic drugs (DMARDs) **(10)**. Over 12 months, a BMD decrease at the spine and trochanter was observed (-2.4 [0.8] vs. -0.6 [0.4] g/cm2, p<0.05 in the spine and -4.3 [0.8] vs. -0.4 [0.5] g/cm2, p<0.001 in the trochanter). Importantly, only disease activity was significantly associated with lumbar BMD decrease, and suppression of disease activity stabilised this bone loss **(10)**. Indeed, DMARDs, as methotrexate and biotherapies (as anti-TNFα), have proved to be able to control inflammation and to arrest BMD loss over time.

Bone remodeling and biochemical markers

Bone remodeling markers and serum cytokines are surrogates to evaluate bone formation, resorption, and further risk of BMD loss, although their interpretation is related to the concomitant use of GCs, DMARDS and biotherapies. High baseline levels of bone resorption markers predict both an increased risk of radiologic progression and BMD loss in patients with RA suggesting that bone loss and erosions are two sides of a similar phenomenon driven by generalized inflammation **(2)**. Indeed, RA therapies, such as biotherapies, are able to arrest bone erosions and bone loss, and these effects have been demonstrated by variations in bone remodeling markers during the course of treatment. In patients receiving an anti-TNFα, serum CTX, and RANK-L decrease dramatically, in parallel with a decrease in disease activity score and a benefit on BMD change **(11)**.

Bone quality

Bone remodelling is mainly carried out by osteoblasts (bone formation) and osteoclasts (bone resorption). Osteoblasts are responsible for the production of type I collagen (organic matrix) and constituents of mineral matrix. The main determinants in the mechanical properties of bone are the amount of mineral in the tissue, the collagen content, the orientation of the collagen fibres and minerals, and the accumulation of microcracks in the bone matrix. Therefore, in RA, there are fundamental changes in the remodeling process of bone that potentially lead to bone structural and mechanical property alterations. It has recently been demonstrated in an animal model of arthritis (SKG and BALB/c mice) that there is a reduction in bone density and a change in the pattern of the collagen organisation **(12)**. In this model, mechanical testing has shown that arthritic femurs have impairment of bone mechanical properties (namely stiffness, ductility and strength). Furthermore, the loss of the mechanical properties in bone was associated with an imbalance in biochemical bone markers and collagen arrangement disturbances indicating that the organization of the collagen component of bone is affected by the inflammatory process **(12)**. A histomorphometric study has been realised in 66 patients with RA **(13)**. There were significant decreases in bone volume, mean wall thickness, mineral apposition rate, number of osteoclasts, osteoclast surface area, and increases in resorption surfaces **(13)**.

Need for further imaging

Although aBMD by DXA can be used for fracture risk assessment in patients with RA, it may underestimate the true fracture probability. Furthermore, the Fracture Risk Assessment Tool (FRAX®) may also show similar deficiencies **(14)**. Consequently, better fracture prediction is required and may occur through more detailed structural imaging. This is one of the major reasons why investigators have recently undertaken research using HR-pQCT.

**Methods of assessing bone micro-architecture by HR-pQCT**

High-resolution peripheral quantitative computed tomography is a non-invasive, low-radiation method for assessing bone microarchitecture and volumetric bone mineral density (vBMD) in cortical and trabecular compartments of the distal radius and tibia **(4)**. The technique was introduced in the mid-2000s and currently, only one commercial HR-pQCT machine, the XtremeCT (SCANCO Medical AG, Brüttisellen, Switzerland), is available **(Figure 1)**. Its application has enhanced understanding of age-related changes and sex differences in bone microarchitecture. Regarding fracture risk assessment, there is evidence that HR-pQCT is generally superior to DXA for discriminating men and women with and without fractures, especially at the sites of measure. Moreover, data from recent studies have provided interesting insights into the effect of new and existing osteoporosis medications on bone structure and strength assessed by HR-pQCT. It also provides information about the pathogenesis of osteoporosis related to menopause or various diseases. **(4, 15)**.

Standard scanning regions: for tibial HR-pQCT, a single dorsal-palmar projection image of the distal tibia is acquired as a scout view and the reference line is set along the plateau found approximately half way along the tibial endplate. The scan is usually commenced 22.5mm proximal to this point. For radial HR-pQCT, the scout view is reviewed and the reference line is set along the plateau located approximately one third to halfway along the radial endplate. Imaging is commenced 9.5mm proximal to this point **(Figure 2a and 2b)**.

When assessments are made of the distal radius and tibia, several variables are created including total, cortical and trabecular area (To.area, Ct.area and Tb.area respectively), and cortical thickness (Ct.Th) **(4)**. Density is calculated in the bone as a whole; the cortical and trabecular regions (Ct.vBMD and Tb.vBMD); and the inner 60% and outer 40% of the trabecular region separately. The ratio of outer trabecular density to inner trabecular density is then calculated. The proportion of Tb.area that constitutes bone tissue is also determined (bone volume/tissue volume, BV/TV). Trabecular microarchitecture is assessed in terms of trabecular thickness (Tb.Th), number (Tb.N), and separation (Tb.Sp) although only Tb.N is measured directly. More recently, a technique was developed by Burghardt *et al.* **(16)** to more accurately delineate the cortical region. Using this technique, a more extensive assessment of the cortex can be made, including parameters such as cortical porosity (Ct.Po).

**Results of HR-pQCT methodology in rheumatoid arthritis**

More recently, HR-pQCT has been used for the assessment of bone damage in patients with chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA). Indeed, RA is characterised by local and systemic bone loss caused by increased bone resorption **(17)**. Many factors, such as excessive production of pro-inflammatory cytokines, result in both periarticular and generalized bone loss **(18)**. The utilisation of HR-pQCT has enhanced our understanding of RA-related changes in bone geometry and bone microarchitecture. Moreover, it allows the detection of inflammation‐related periarticular bone erosions at the hand **(19)** which is of particular importance as these lesions are a key feature of RA, reﬂect irreversible damage to the affected joints, and closely relate to functional impairment **(19) (Figure 1)**.

**Comparison of volumetric bone mineral density and microarchitecture in RA patients and controls at the metacarpal head**

The first study evaluating the ability of HR-pQCT to assess vBMD and microarchitecture in patients with RA was published by Fouque-Aubert *et al.* in 2010 **(20)**. The microarchitecture impairment was evaluated in patients with RA (2 subgroups: early RA with disease duration ≤2 years, n=36 and late RA with disease duration >3years, n=57) in comparison with healthy controls at metacarpal heads (MCH) 2 and 3. Firstly, the whole RA group was compared to the healthy controls: patients with RA had significantly lower Tb.vBMD and Tb.Th at both MCHs (p<0.05 for all) with or without adjustment for age. Secondly, comparison of the patients with early RA, patients with late RA and healthy controls was realized: a significant difference between controls, patients with early and late RA was found for Tb.vBMD and Ct.vBMD at MCH2 and for Tb.Th at both MCHs. Trabecular thickness was reduced at MCH2 and MCH3 in patients with late RA (p<0.05) and at MCH3 in patients with early RA (p<0.05) compared to healthy controls. For these parameters, patients with early and late RA did not differ significantly. Thirdly, Tb.vBMD and Tb.Th were negatively correlated with the disease activity characterised by disease activity score on 28 joints (DAS28), Erythrocyte sedimentation rate (ESR) and C reactive protein. There were no significant associations between HR-pQCT parameters and age, disease duration, Sharp score, Anti-Citrullinated Peptide Antibody (ACPA) status and various treatments, such as disease modifying anti-rheumatic drugs (DMARDs) and tumor necrosis factor alpha inhibitors (TNFi).

In a more recent study, vBMD and microarchitecture at MCH2 was compared to that at the distal radius (DR) in patients with RA in a cross-sectional study of 100 female patients (53.4 ±9.3 years) **(21)**. There were significant correlations in vBMD and microarchitectural parameters between the two sites (r = 0.201-0.628, p<0.05 for all). Interestingly, a new protocol was recently developed in 12 non-RA patients to evaluate vBMD and microarchitecture at MCH 2 and 3, metacarpal shaft (MCS) 2 and 3, and the ultra-ultra-distal radius, three sites commonly affected in RA **(22)**. This protocol extends the potential for *in vivo* HR-pQCT imaging in the assessment of patients with RA. However, further evaluation of precision and feasibility for this modality is required.

**Comparison of volumetric bone mineral density and microarchitecture in RA patients and controls at the distal radius**

Several studies have used HR-pQCT to evaluate vBMD and microarchitecture at the DR in patients with RA (male and female) and compared this to healthy controls **(23-25)** **(Table 1)**. Both trabecular and cortical bone were severely affected in male and female patients with RA **(Table 2)**. Average Ct.vBMD (ranging from -3.5% to -11.7%) and Tb.vBMD (ranging from -6.9% to -24.0%) values were significantly lower in RA patients than controls (p<0.05 for all) **(23-25).** At the DR, most of the trabecular microstructural indices, such as BV/TV, Tb.N and Tb.Th, were lower in male and female RA patients, when compared with healthy sex-matched controls **(Table 2)**. In studies by Zhu *et al* **(23, 24)**, Ct.Th was similar in patients and controls whereas Ct.Po was significantly higher in patients. Conversely, Ct.Th was lower in male and female RA patients in study by Kocijan *et al* **(25)** with a difference in Ct.Po shown only in men **(Table 2)**.

**Factors influencing HR-pQCT parameters at the distal radius in patients with RA**

Demographics and disease activity/severity

In addition to demographics, factors independently associated with vBMD and microarchitectural parameters at the DR in patients with RA were mostly related to disease activity/severity. In the study by Kocijan et al. **(25)**, bone geometric parameters including cortical perimeter (Ct.Pm, mm), cortical area (Ct.Area, mm2), and trabecular area (Trab.Area, mm2) were evaluated using the standard analysis protocol. Cortical perimeter was defined as the outer boundary of the periosteal surface, mm. Cortical perimeter was independently influenced by age (β=0.20, t=2.91, p=0.005), sex (β=-0.38, t=3.98, p<0.0001), and height (β=0.40, t=3.70, p=0.0001). Cortical thickness was significantly related to age (β=-0.33, t=3.00, p=0.004). Trabecular number was inversely related to disease duration (β=-0.23, t=2.27, p=0.045), but not to the age, highlighting a possible loss of trabecular bone during disease. For Zhu *et al* **(23)**, most of the differences between RA patients and controls did not depend on menstrual status, indicated by the majority of interactive p-values >0.05, and there were no significant differences in vBMD, microstructural, and mechanical indices between RA patients with and without active swollen wrist(s) at the time of study. Zhu *et al* **(24)** did show a significant association between HR-pQCT parameters and indices of overall and local disease activity (higher ESR and DAS28 score) and severity (longer disease duration and higher number of deformed joints), as well as with serum levels of several pro-inflammatory cytokines (TNFα, IL1β and IL6). Interestingly, functional status and erosive disease were independent explanatory variables associated with Tb.vBMD and microarchitecture (BV/TV, Tb.N, and Tb.Sp), while the number of deformed joints was independently associated with Ct.vBMD **(21)**. Furthermore, C-reactive protein level was shown to be independently associated with Ct.vBMD. No clinical factors were independently associated with Ct.Th, Tb.Th, or inhomogeneity of the trabecular network.

Glucocorticoids exposure and anti-rheumatic therapies

Interestingly, in several studies **(21, 23-25)**, there were no significant differences in HR-pQCT parameters at the DR between RA patients who were and were not exposed to glucocorticoids (GCs) including when use of oral GCs, cumulative dose, and duration of oral GCs were assessed. However, other anti-rheumatic therapies may influence bone quality in RA. Specifically, biological agents such as TNFi were reported to arrest bone loss or even to increase areal BMD **(26, 27)**. However, a definite benefit on the prevention of osteoporosis or fractures has not yet been shown, and their influence on bone microstructure and geometry in humans remains unclear. Furthermore, little is known about the influence of conventional DMARDs. In a study by Kocijan *et al* **(25)**, current DMARD intake was independently associated with a greater cortical perimeter (p=0.018) and smaller Ct.Th (p=0.026) at the DR. In contrast, a trend was found between use of biological agents and lower cortical perimeter (p=0.08). However, Zhu *et al* **(21)** found that factors related to treatment, including use of DMARDs, number of current DMARDs and use of biologics, did not influence vBMD nor microarchitectural parameters at the DR. In summary, the net effect of GCs and anti-rheumatic therapies on vBMD and bone microarchitecture in RA patients remains to be determined.

Comparison of bone microarchitecture in RA and Psoriatic Arthritis

Kocijan *et al.* **(28)** performed a detailed comparative analysis of vBMD and microarchitecture using HR-pQCT at the DR in 110 patients (60 RA, 50 PsA). No significant differences were found between PsA and RA patients for trabecular and cortical vBMD and for all the parameters related to cortical and trabecular bone microstructure. Comparison between seropositive RA patients (RA+) and seronegative RA patients (RA-) revealed that (i) Tb.vBMD and BV/TV were significantly decreased in RA+ as compared to their RA- counterparts, and (ii) no significant differences in Ct.vBMD, Ct.Th or Ct.Po were found among RA+ and RA-. These data suggest that, unlike cortical bone, Tb.vBMD and trabecular microarchitecture are more severely affected in RA+ patients.

In summary, both trabecular and cortical bone are deficient in patients with RA compared to healthy controls at both periarticular and non-periarticular sites but whether these deficits are indeed related to the fracture risk in RA has not been fully elucidated. Consequently, the usefulness of these indices in fracture prediction is currently uncertain..

**Detection of structural bone lesions**

The first pilot studies evaluated the use of HR-pQCT for the differentiation of inflammatory joint disease, such as RA and psoriatic arthritis (PsA), **(29)** and degenerative changes **(30)** respectively. Metacarpal (MCP) joints of the second, third, and fourth digits (2-4) of the predominantly affected hand were evaluated for the presence and size of bone erosions, as well as osteophytes and cortical thinning.

In the first study completed by Stach *et al.* **(30)**, 56 RA patients and 30 healthy individuals underwent HR-pQCT of the proximal wrist and MCP joints. Lesions were quantified and their exact localizations were recorded. Important findings were: (i) HR-pQCT could detect bone erosions <0.5 mm in width or depth. Although small erosions could be observed in healthy individuals as well as RA patients, lesions >1.9 mm in diameter were highly specific for RA (p=0.008). (ii) Bone erosions were mostly found along the radial sites of the MCHs 2 and 3. (iii) No significant difference in the presence of osteophytes between the 2 groups was found but cortical thinning was more pronounced in RA patients.

Thereafter, 58 RA patients and 30 PsA patients underwent HR-pQCT **(29)**. Patients with PsA and RA had the same number of bone erosions (6.3 ±1.3 vs. 6.1 ±0.9 respectively), but they were less severe and overall smaller in size and depth in PsA (diameter of >1.9 mm, p<0.001). Erosions in PsA were mostly tubule-shaped or had a narrow neck at the entrance to the anomaly, whereas U-shaped lesions, with a wider entrance, were more typical in RA. Erosions in PsA were more evenly distributed, lacking the strong preponderance for the radial sites found in RA. Osteophytes were increased in number (16% vs. 100%), extent and size in PsA as compared with RA, often affecting the entire circumference of bone (‘bony corona’). The key determinants of the periarticular bone anomalies in patients with RA were: disease duration for bone erosions **(30, 31)**, disease activity (DAS28 and C-reactive protein) for cortical thinning **(30)** and bone alkaline phosphatase **(31)** and age for osteophytosis **(30, 31)**.

In an effort to standardize HR-pQCT for this utility, Srikhum *et al.* **(32)** and Topfer *et al.* **(33)** developed new quantitative bone erosions measures, which were simpler and less time-consuming, than the usual methods, and thus were more amenable to clinical use. However, their sample sizes were small (16 and 18 patients with RA respectively). At a similar time, a methodology to measure three dimensional (3D) joint space widths in the small joints of patients with RA was developed and this is awaiting evaluation in larger studies **(34-37)**.

**Comparison of bone erosion assessment by HR-pQCT with other imaging techniques**

Comparative studies of HR-pQCT and other techniques, such as MRI and high-resolution ultrasonography (US), in the assessment of bone erosions, have been recently performed **(38-40)**. Albrecht *et al.* **(38)** compared HR-pQCT and MRI in terms of sensitivity and specificity of bone erosion detection and erosion size at the MCP joints (2-4) of 50 RA patients (12 regions, 4 per joint, 600 evaluated joint regions). A total of 111 joint regions showed erosions on MRI and 137 using HR-pQCT. In 28 regions false negative lesions (MRI negative, HR-pQCT positive) were found, all of which were very small lesions (volume <10 mm³), and 2 results were felt to be false-positives (HR-pQCT negative, MRI positive). Previously, a detailed comparative analysis of the use of high-resolution US and HR-pQCT to assess bone erosions in patients with RA (n=14) and PsA (n=6), as well as healthy individuals (n=6) was carried out **(39)**. Results were quite disappointing because false-negative assessments (US negative, HR-pQCT positive) were found in 9.9% of the joint regions investigated whereas false-positive results (US positive, HR-pQCT negative) were found in 28.6%.

HR-pQCT can depict many bone and joint abnormalities. Specifically, it can assess the size, number, and shape of erosions; the presence of bone surface lesions and osteophytes; and the width of the joint space. Techniques used can be automated or semi-automated with customized scanning cast and seating positions as necessary. As part of this assessment, it can depict very small erosions and this is at variance with some lower resolution techniques. However, the relevance of these tiny abnormalities within the disease course or diagnosis is as yet unclear. In contrast, MRI has been extensively validated in the assessment of RA. It assesses not only bone lesions but also soft tissue lesions like bone marrow oedema which is highly correlated with occurrence of new erosions. In a study by Albrecht *et al.* **(38)** comparing MRI and HR-pQCT, the false positive rate of MRI was relatively low and all the false negatives related to the especially small lesions with unknown clinical significance. There is therefore potential evident for the use of HRpQCT but consensus regarding its superiority is lacking. Similarly, HR-pQCT may clearly be superior to US in terms of detecting erosions at the hand/wrist joints but it is unable to examine larger, more proximal joints such as the elbow and knee. There are therefore benefits and limitations of each technique.

**Impact of treatment in rheumatoid arthritis assessed by HR-pQCT**

DMARDs and biologic agents are established therapies for reducing RA joint damage and are widely used in daily clinical practice. Using HR-pQCT for monitoring responses to therapy is of great interest as prevention of bone erosions is of paramount importance in the treatment of RA. Finzel *et al* showed that HR-pQCT allowed longitudinal monitoring of individual bone erosions and their responsiveness to methotrexate (MTX), TNFi **(41)** and interleukin-6 receptor inhibition (IL6-Ri) **(42)**.

The first longitudinal study **(41)** identified 27 erosions in the MCP joints (2-4) of 30 RA patients treated with TNFi in combination with MTX (mean dose of 15.5 mg/week) and 21 sex, age and disease activity- matched patients treated with MTX monotherapy (mean dose of 15.4 mg/week). All erosions were assessed for maximal width and depth at baseline and after 1 year. At baseline, the mean width and depth of bone erosions in the TNFi group was not signiﬁcantly different from the MTX-treated group (width: TNFi 2.04 ±0.14 vs. MTX 2.4 ±0.23 mm; depth: TNFi 2.3 ±0.25 vs. MTX 2.4 ±0.24 mm). Furthermore, all bone erosions detected at baseline could be visualised at follow-up after 1 year. The mean depth of erosions signiﬁcantly decreased after 1 year of treatment with TNFi (−0.10 ±0.04 mm, p=0.019), whereas their width remained unchanged. Interestingly, the reduction in the depth of lesions was conﬁned to erosions showing evidence of sclerosis at the base of the lesion. In contrast, mean depth and width of erosive lesions increased in the methotrexate-treated group (+0.17 ±0.06 mm, p=0.005 and +2.16 ±0.24 mm, p<0.001 respectively).

Another longitudinal study completed by Finzel *et al.* **(42)** included 20 RA patients treated with IL6-Ri, tocilizumab, in combination with MTX (mean dose of 12.9 mg/week). Results had shown that use of tocilizumab was also associated with repair of bone erosions in patients with RA. Interestingly, repair was based on reduction in the depth and width, although the former did not reach statistical significance. However, the repair of bone erosions was limited, as with TNFi, and did not lead to complete healing. Lastly, Finzel *et al.* **(43)** investigated whether MTX monotherapy (n=13, mean dose of 16.6 mg/week) or TNFi monotherapy (n=28) affected osteophyte formation and bone erosions in patients with PsA. At 1-year follow-up, the size of the osteophytes had progressed in PsA patients treated with either methotrexate (+54.3%) or TNFi (+61.1%), whereas clinical disease activity decreased, and mean depth and width of erosive lesions did not progress in either group.

**Conclusions**

In this review, we report that HR-pQCT is a useful method for depicting bone erosions and other forms of cortical bone lesions, such as osteophytes and cortical thinning, in patients with RA. Furthermore, imaging of the distal radius and MCHs simultaneously allows assessment of trabecular and cortical bone parameters, which have both shown precise and reproducible associations with fracture. Future avenues of research should include using HR-pQCT evaluation of joint and bone changes in other systemic inflammatory arthritides, such as ankylosing spondylitis **(44, 45)** and systemic lupus erythematous **(46-49)**. It should be noted, however, that the technique remains predominantly a research tool which is under assessment for clinical utilisation, with further investigation and appropriate training required before consideration of more routine clinical use. Studies are most needed to evaluate the relevance of (i) bone abnormalities (cortical and trabecular) in the occurrence of fractures and (ii) the small-erosions described in the disease course or in the diagnosis of the RA.

**Tables and Figures**

Table 1: Studies with high resolution peripheral qualitative computed tomography assessment at the distal radius in patients with RA.

Table 2: Volumetric BMD and microstructure by HR‐pQCT at the distal radius in male and female RA patients and Controls.

Figure 1: Radial high-resolution peripheral quantitative computed tomography (A) imaging procedure (B) HRpQCT of the distal radius (C) radial erosions in the third metacarpophalangeal joint in patients with RA (coronal plane).

Figure 2: Standard scanning regions, scout views for (a) tibial and (b) radial HRpQCT scan.

**References**

(1) McCloskey E, Kanis JA. FRAX updates 2012. Curr Opin Rheumatol. 2012;24:554-60.

(2) Roux C. Osteoporosis in inflammatory joint diseases. Osteoporos Int. 2011;22:421-33.

(3) Ohrndorf S, Werner SG, Finzel S, Backhaus M. Musculoskeletal ultrasound and other imaging modalities in rheumatoid arthritis. Curr Opin Rheumatol. 2013:25:367-74.

(4) Cheung AM, Adachi JD, Hanley DA, et al. High-resolution peripheral quantitative computed tomography for the assessment of bone strength and structure: a review by the Canadian Bone Strength Working Group. Curr Osteoporos Rep. 2013;11:136-46.

(5) 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;54:3104-12.

(6) Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995;54:49–52.

(7) Kim SY, Schneeweiss S, Liu J, Daniel GW, Chang CL, Garneau K, et al. Risk of osteoporotic fracture in a large population-based cohort of patients with rheumatoid arthritis. Arthritis Res Ther. 2010;12:R154.

(8) El Maghraoui A1, Rezqi A, Mounach A, Achemlal L, Bezza A, Ghozlani I. Prevalence and risk factors of vertebral fractures in women with rheumatoid arthritis using vertebral fracture assessment. Rheumatology (Oxford). 2010;49:1303-10.

(9) Vis M, Haavardsholm EA, Bøyesen P, Haugeberg G, Uhlig T, Hoff M, Woolf A, Dijkmans B, Lems W, Kvien TK. High incidence of vertebral and non-vertebral fractures in the OSTRA cohort study: a 5-year follow-up study in postmenopausal women with rheumatoid arthritis. Osteoporos Int. 2011;22:2413-9.

(10) Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. Lancet. 1994;344:23-7.

(11) Vis M, Havaardsholm EA, Haugeberg G, Uhlig T, Voskuyl AE, van de Stadt RJ, et al. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2006;65:1495-99.

(12) Abdulghani S, Caetano-Lopes J, Canhão H, Fonseca JE. Biomechanical effects of inflammatory diseases on bone-rheumatoid arthritis as a paradigm. Autoimmun Rev. 2009;8:668-71.

(13) Pérez-Edo L, Díez-Pérez A, Mariñoso L, Vallés A, Serrano S, Carbonell J. Bone metabolism and histomorphometric changes in rheumatoid arthritis. Scand J Rheumatol. 2002;31:285-90.

(14) Broy SB, Tanner SB; FRAX(®)Position Development Conference Members. Official Positions for FRAX® clinical regarding rheumatoid arthritis from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®. J Clin Densitom. 2011;14:184-9.

(15) Geusens P, Lems WF. Osteoimmunology and osteoporosis. Arthritis Res Ther. 2011;13:242.

(16) Burghardt AJ, Kazakia GJ, Majumdar S. A local adaptive threshold strategy for high resolution peripheral quantitative computed tomography of trabecular bone. Ann Biomed Eng 2007;35:1678-86.

(17) Geusens P, Chapurlat R, Schett G, Ghasem-Zadeh A, Seeman E, de Jong J, van den Bergh J. High-resolution in vivo imaging of bone and joints: a window to microarchitecture. Nat Rev Rheumatol. 2014;10:304-13.

(18) Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol. 2012;8:656-664.

(19) Geusens PP, Finzel S. Imaging: Bone erosions in rheumatoid arthritis: better to see more? Nat Rev Rheumatol. 2013;9:385-386.

(20) Fouque-Aubert A, Boutroy S, Marotte H, et al. Assessment of hand bone loss in rheumatoid arthritis by high-resolution peripheral quantitative CT. Ann. Rheum. Dis. 2010;69:1671-1676.

(21) Zhu TY, Griffith JF, Qin L, et al. Bone density and microarchitecture: relationship between hand, peripheral, and axial skeletal sites assessed by HR-pQCT and DXA in rheumatoid arthritis. Calcif Tissue Int. 2012;91:343-55.

(22) Feehan L, Buie H, Li L, McKay H. A customized protocol to assess bone quality in the metacarpal head, metacarpal shaft and distal radius: a high resolution peripheral quantitative computed tomography precision study. BMC Musculoskelet Disord. 2013;14:367.

(23) Zhu TY, Griffith JF, Qin L, et al. Structure and strength of the distal radius in female patients with rheumatoid arthritis: a case–control study. J. Bone Miner. Res. 2013;28:794-806.

(24) Zhu TY, Griffith JF, Qin L, et al. Alterations of Bone Density, Microstructure and Strength of the Distal Radius in Male Patients with Rheumatoid Arthritis: A Case-Control Study with HR-pQCT. J Bone Miner Res. 2014 Mar 18. doi: 10.1002/jbmr.2221.

(25) Kocijan R, Finzel S, Englbrecht M, Engelke K, Rech J, Schett G. Decreased quantity and quality of the periarticular and nonperiarticular bone in patients with rheumatoid arthritis: a cross-sectional HR-pQCT study. J Bone Miner Res. 2014;29:1005-14.

(26) Marotte H, Pallot-Prades B, Grange L, Gaudin P, Alexandre C, Miossec P. A 1-year case-control study in patients with rheumatoid arthritis indicates prevention of loss of bone mineral density in both responders and nonresponders to infliximab. Arthritis Res Ther. 2007;9:R61.

(27) Lange U, Teichmann J, Muller‐Ladner U, Strunk J. Increase in bone mineral density of patients with rheumatoid arthritis treated with anti‐TNF‐alpha antibody: a prospective open‐label pilot study. Rheumatology (Oxford). 2005;44:1546–8.

(28) Kocijan R, Finzel S, Englbrecht M, Engelke K, Rech J, Schett G. Differences in bone structure between rheumatoid arthritis and psoriatic arthritis patients relative to autoantibody positivity. Ann Rheum Dis Aug 7. doi: 10.1136/annrheumdis-2013-203791.

(29) Finzel S, Englbrecht M, Engelke K, Stach C and Schett G. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. Ann Rheum Dis. 2011;70:122-127.

(30) Stach CM, Bäuerle M, Englbrecht M, et al. Periarticular bone structure in rheumatoid arthritis patients and healthy individuals assessed by high-resolution computed tomography. Arthritis Rheum. 2010;62:330-339.

(31) Aschenberg S, Finzel S, Schmidt S, et al. Catabolic and anabolic periarticular bone changes in patients with rheumatoid arthritis: a computed tomography study on the role of age, disease duration and bone markers. Arthritis Res Ther. 2013;15:R62.

(32) Srikhum W, Virayavanich W, Burghardt AJ, et al. Quantitative and semiquantitative bone erosion assessment on high-resolution peripheral quantitative computed tomography in rheumatoid arthritis. J. Rheumatol. 2013;40:408-416.

(33) Töpfer D, Finzel S, Museyko O, Schett G, Engelke K. Segmentation and quantification of bone erosions in high-resolution peripheral quantitative computed tomography datasets of the metacarpophalangeal joints of patients with rheumatoid arthritis. Rheumatology (Oxford). 2014;53:65-71.

(34) Barnabe C, Feehan L; SPECTRA (Study GrouP for XTrEme-CT in RA). High-resolution peripheral quantitative computed tomography imaging protocol for metacarpophalangeal joints in inflammatory arthritis: the SPECTRA collaboration. J Rheumatol. 2012;39:1494-5.

(35) Barnabe C, Szabo E, Martin L, Boyd SK, Barr SG. Quantification of small joint space width, periarticular bone microstructure and erosions using high-resolution peripheral quantitative computed tomography in rheumatoid arthritis. Clin. Exp. Rheumatol. 2013;31:243-250.

(36) Barnabe C, Buie H, Kan M, et al. Reproducible metacarpal joint space width measurements using 3D analysis of images acquired with high-resolution peripheral quantitative computed tomography. Med Eng Phys. 2013;35:1540-4.

(37) Burghardt AJ, Lee CH, Kuo D, et al. Quantitative in vivo HR-pQCT imaging of 3D wrist and metacarpophalangeal joint space width in rheumatoid arthritis. Ann Biomed Eng. 2013;41:2553-64.

(38) Albrecht A, Finzel S, Englbrecht M, et al. The structural basis of MRI bone erosions: an assessment by micro CT. Ann. Rheum. Dis. 2013;72:1351-1357.

(39) Finzel S, Ohrndorf S, Englbrecht M, et al. detailed comparative study of high-resolution ultrasound and micro-computed tomography for detection of arthritic bone erosions. Arthritis Rheum. 2011;63:1231-6

(40) Teruel JR, Burghardt AJ, Rivoire J, et al. Bone Structure and Perfusion Quantification of Bone Marrow Edema Pattern in the Wrist of Patients with Rheumatoid Arthritis: A Multimodality Study. J Rheumatol. 2014 Aug 1. pii: jrheum.131564. [Epub ahead of print].

(41) Finzel S, Rech J, Schmidt S, et al. Repair of bone erosions in rheumatoid arthritis treated with tumour necrosis factor inhibitors is based on bone apposition at the base of the erosion. Ann. Rheum. Dis. 2011;70:1587-1593.

(42) Finzel S, Rech J, Schmidt S, Engelke K, Englbrecht M, Schett G. Interleukin‑6 receptor blockade induces limited repair of bone erosions in rheumatoid arthritis: a micro CT study. Ann. Rheum. Dis. 2013;72:396-400.

(43) Finzel S, Kraus S, Schmidt S, et al. Bone anabolic changes progress in psoriatic arthritis patients despite treatment with methotrexate or tumour necrosis factor inhibitors. Ann. Rheum. Dis. 2013;72:1176-1181.

(44) Klingberg E, Lorentzon M, Göthlin J, et al. Bone microarchitecture in ankylosing spondylitis and the association with bone mineral density, fractures, and syndesmophytes. Arthritis Res Ther. 2013;15:R179.

(45) Zhu TY, Griffith JF, Qin L, et al. Density, structure, and strength of the distal radius in patients with psoriatic arthritis: the role of inflammation and cardiovascular risk factors. Osteoporos Int. 2014 Aug 27. [Epub ahead of print].

(46) Li EK, Zhu TY, Tam LS, et al. Bone microarchitecture assessment by high-resolution peripheral quantitative computed tomography in patients with systemic lupus erythematosus taking corticosteroids. J Rheumatol. 2010;37:1473-9.

(47) Tang XL, Griffith JF, Qin L, et al. SLE disease per se contributes to deterioration in bone mineral density, microstructure and bone strength. Lupus. 2013;22:1162-8.

(48) Tang XL, Zhu TY, Hung VW, et al. Increased organ damage associated with deterioration in volumetric bone density and bone microarchitecture in patients with systemic lupus erythematosus on longterm glucocorticoid therapy. J Rheumatol. 2012;39:1955-63.

(49) Tang XL, Qin L, Kwok AW, et al. Alterations of bone geometry, density, microarchitecture, and biomechanical properties in systemic lupus erythematosus on long-term glucocorticoid: a case-control study using HR-pQCT. Osteoporos Int. 2013;24:1817-26.