

# Heterogeneity of Cortical Breaks in Hand Joints of Patients with Rheumatoid Arthritis and Healthy Controls Imaged by High-resolution Peripheral Quantitative Computed Tomography

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**ABSTRACT. Objective.** Conventional radiographs (CR) of the hands are the gold standard for imaging bone erosions. The presence of bone erosions, reflected by the presence of cortical breaks, is a poor prognostic factor in patients with rheumatoid arthritis (RA). The availability of high-resolution peripheral quantitative computed tomography (HR-pQCT) enables detailed investigation of cortical breaks in rheumatic diseases. The aim of this image review is to show HR-pQCT images of the spectrum of cortical breaks with and without underlying trabecular bone changes in metacarpophalangeal (MCP) joints of healthy controls (HC) and patients with RA, with corresponding images on CR and magnetic resonance imaging (MRI).

**Methods.** Second and third MCP joints of 41 patients (of which 10 were early RA with  $\leq 2$  years and 24 longstanding RA with  $\geq 10$  years of disease duration) and 38 HC were imaged by CR, MRI, and HR-pQCT (XtremeCT1, Scanco Medical AG). Representative images of the spectrum of cortical breaks were selected.

**Results.** Cortical breaks were found in early and longstanding RA, but also in HC. They were heterogeneous in size, location, and number per joint, with a variety of surrounding cortical and underlying trabecular bone characteristics.

**Conclusion.** Using HR-pQCT images of MCP joints, heterogeneous cortical breaks with and without surrounding trabecular bone changes were found, not only in RA but also in HC. The underlying mechanisms and significance of this spectrum of cortical breaks as found with high 3-D resolution needs further investigation. (J Rheumatol 2016;43:1914–20; doi:10.3899/jrheum.160646)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS

BONE

COMPUTED TOMOGRAPHY

Bone is one of the critical supporting structures of a normally functioning joint. In normal conditions, the only well-documented periarticular cortical breaks are related to the presence of blood vessels that perforate bone from the

periosteum toward the bone marrow at the epiphyses<sup>1</sup>. In rheumatoid arthritis (RA), pathological cortical breaks, i.e. erosions, can occur in the joints. Complex physical, cellular, and molecular interactions between bone and the immune

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As part of a supplement series from SPECTRA on HR-pQCT, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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system, termed osteoimmunology, drive the development of bone erosions through activation of osteoclasts<sup>2</sup>. In early RA, osteoclasts are locally activated by inflammation occurring at the synovium. An alternative hypothesis is that the osteoclasts are activated within the bone marrow by anticyclic citrullinated protein antibodies<sup>3</sup>. Osteoclast activation is the final pathway that results in disruption of the bone matrix, mainly at sites not protected by cartilage and at ligament insertions, thus allowing a direct anatomical connection between the joint space and the immune system in the bone marrow, in addition to normal vascular connections at the epiphyses<sup>1</sup>. Second and third metacarpophalangeal (MCP) joints are among the first hand joints affected in the early disease course of RA, with the ulnar and radial side of these joints most commonly involved, as demonstrated on conventional radiographs (CR)<sup>4</sup>. Additional damage can ensue if the inflammatory cascade is not suppressed with therapy. Later in the course of RA, the increasing size of cortical breaks — which rarely heal in RA — contributes to joint damage and loss of function<sup>5,6</sup>.

In RA, the presence, size, and number of cortical breaks, defined as erosions on CR, are poor prognostic factors, and influence the aggressiveness of treatment required<sup>4</sup>. Prevention of these cortical breaks and their progression is one of the major endpoints in clinical trials<sup>5</sup>. Currently, CR of the hands and feet are the gold standard for imaging erosions in both research and clinical practice settings<sup>4,7,8,9</sup>. CR is widely available, fast to perform, cheap, and easy to use<sup>10</sup>. Scoring of those bone erosions on radiographs has a long history of interpretation and standardization<sup>9</sup>. Scoring methods include simple counts of the presence and number of bone erosions, and scoring levels for their size<sup>9</sup>. Limitations of radiography include floor effects (i.e., radiographic visualization of erosions may occur late in the disease) and ceiling effects (i.e., progression can occur even after the highest radiographic damage score has been assigned), slow change over time, and superimposition<sup>9</sup>. Further, scoring can be time consuming.

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a noninvasive imaging technique. Its spatial resolution allows detailed evaluation of the 3-D cortical and trabecular bone (combined as well as separately). For a standard scan of 9 mm, the radiation dose is < 3 µSv. It has been applied for assessment of bone damage in rheumatic diseases affecting the hand joints<sup>11</sup>. In RA, this technology has been shown to be more sensitive than CR for identifying cortical breaks<sup>12</sup>. In addition, HR-pQCT can detect small cortical breaks and exactly localize and measure individual cortical breaks in 3-D, thereby facilitating the monitoring of their development and investigating the effects of antiinflammatory therapies<sup>12,13,14</sup>.

The aim of the present HR-pQCT image review is to show the spectrum of cortical breaks on selected images of cortical and subchondral trabecular bone of MCP joints of patients

with RA and healthy controls (HC), with corresponding images on CR and magnetic resonance imaging (MRI). In RA, when scoring periarticular bone destruction using CR and MRI, cortical breaks are considered bone erosions and vice versa. In our presentation, for HR-pQCT, we use the term “cortical break” to refer to an image where the cortex is discontinuous, which can be erosions but also vascular channels.

The present review was initiated and supported by SPECTRA (Study group for xtrEme Computed Tomography in Rheumatoid Arthritis, an international collaboration of HR-pQCT users) to expand knowledge and validation in hand joint imaging research in rheumatology<sup>15</sup>.

## MATERIALS AND METHODS

**Participants.** Forty-one patients with RA (of which 10 were early RA of ≤ 2 yrs, and 24 longstanding RA of ≥ 10 yrs of disease duration) and 38 HC were recruited at the Maastricht University Medical Center, the Netherlands. All RA patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA<sup>16</sup>. No HC had hand joint complaints. Baseline and followup (1 yr) measurements of HR-pQCT, MRI, and CR were performed. Demographics, disease duration, and presence of rheumatoid factor and anticyclic citrullinated protein antibody were recorded, if applicable. All patients with RA completed the Dutch version of the Health Assessment Questionnaire<sup>17</sup>. All subjects signed informed consent. Ethical approval was obtained from the ethics board of the Academic Hospital Maastricht, the Netherlands.

**Conventional radiography.** Posterior-anterior radiographs of both hands of the subjects were taken using high-resolution digital radiography (Siemens FD-X 45kV/5mAs) according to a standardized protocol in daily practice.

**HR-pQCT scanning procedure.** Second and third MCP and proximal interphalangeal (PIP) joints of both hands in patients with RA and only the dominant hand in HC were scanned by HR-pQCT (82 µm, XtremeCT1, Scanco Medical AG) according to the standard image acquisition protocol from SPECTRA<sup>15</sup>.

**MRI scanning procedure.** The second and third MCP and PIP joints of both hands were examined using a 3.0 T Achieva Philips MRI device. During the examination, the subject's hand rested in a dedicated wrist coil. The hand was fixed inside the coil and the space around the hand was filled with rubber to reduce motion artefacts. Images were acquired of both hands using axial T1-weighted, axial fat-suppressed T2-weighted and sagittal 3D WATSc sequences. Additional images of the hand with most symptoms (in RA) or dominant hand (HC) were acquired post-intravenous gadolinium (Gadovist 1.0 mmol/ml solution for injection) using axial and coronal fat-suppressed T1-weighted images. Total acquisition time was about 30 min per hand. The MRI images were scored by a radiologist, blinded for clinical data, for the presence of erosions, bone marrow edema (BME), and synovitis.

**Definition of cortical breaks visualized on HR-pQCT.** Regarding the use of CR, several definitions for bone erosions are available from the literature, such as cortical break, discontinuous cortex, or defects in contour on an anteroposterior radiograph<sup>12,14,18,19,20</sup>. Within SPECTRA, a preliminary working definition of cortical breaks on images from HR-pQCT has been developed for application in HR-pQCT. In HR-pQCT imaging, once a cortical break is identified on one slice, it is further specified by examining its presence on adjacent slices and specification of subchondral bone characteristics. A cortical break is considered a bone erosion if it extends over a minimum of 2 consecutive slices in at least 2 perpendicular planes (transverse plane and sagittal or coronal plane); and if it has a nonlinear delineation of the cortical perforation and is accompanied with underlying loss of trabecular structure. A cortical break is considered a vascular channel if it is regularly delineated, without loss of surrounding trabecular structure. A bone

cyst is defined as disproportional area of absence of trabecular bone at the site of a small cortical break.

**Selection procedure.** One person prepared a selection of typically normal images, variants of normal images, and variants of cortical breaks, according to the proposed SPECTRA definition in the MCP joints. Consensus on the final selection of the images and scoring was reached within a team of experts. The corresponding MRI sequences and radiographs were chosen in collaboration with an MRI technician and a musculoskeletal radiologist.

Cases were selected by scrolling through the set of transverse source images from distal to central within the joint (phalangeal base) and proximal to central within the joint (metacarpal head) in a freeware multiplanar reformat DICOM viewer (Osirix v.5.8.5 64-bit). With Osirix, 3 orthogonal planes (transverse, coronal, and sagittal) of each joint can simultaneously be viewed. Using a crossed locator, specific locations of interest can be indicated in 1 plane, and this is also automatically indicated on the images in the other 2 planes, as illustrated in Supplementary Figures 1 and 2, available online at jrheum.org.

The localization of cortical breaks was done as described by Stach, *et al*<sup>12</sup>. The localization includes 4 quadrants in transverse view (palmar, ulnar, dorsal, and radial), the radial and ulnar side in coronal views, and the palmar and dorsal side in sagittal views, both in the metacarpal head and the phalangeal base (Figure 1). In addition, volume measurements can be made

in Osirix. Measuring maximal width and depth of a cortical break is done in transverse and coronal or sagittal plane with lines perpendicular to each other (Supplementary Figure 3, available online at jrheum.org). With HR-pQCT, a 3-D animation of the joint can also be constructed. Two examples of such a 3-D animation of an MCP joint are shown in Supplementary Figures 4 and 5 (available online at jrheum.org). Supplementary Figure 4 shows a normal joint, and Supplementary Figure 5 shows a joint of an RA patient with cortical breaks compatible with bone erosions.

RESULTS

Of the selected subjects, the mean age (SD) of the patients with early RA was 58.5 (0.7) years; patients with long-standing RA: 60.0 (7.0) years; and HC: 53 (13.8) years. The mean (SD) disease duration was 11.5 (10.6) and 226 (84) months for patients with early and longstanding RA, respectively. The mean (SD) Health Assessment Questionnaire scores were 0.31 (0.08) and 1.93 (0.79) for early and longstanding RA, respectively.

In HC, we selected HR-pQCT images of normal bone (Figure 2) and bone with cortical breaks (Figure 3). In

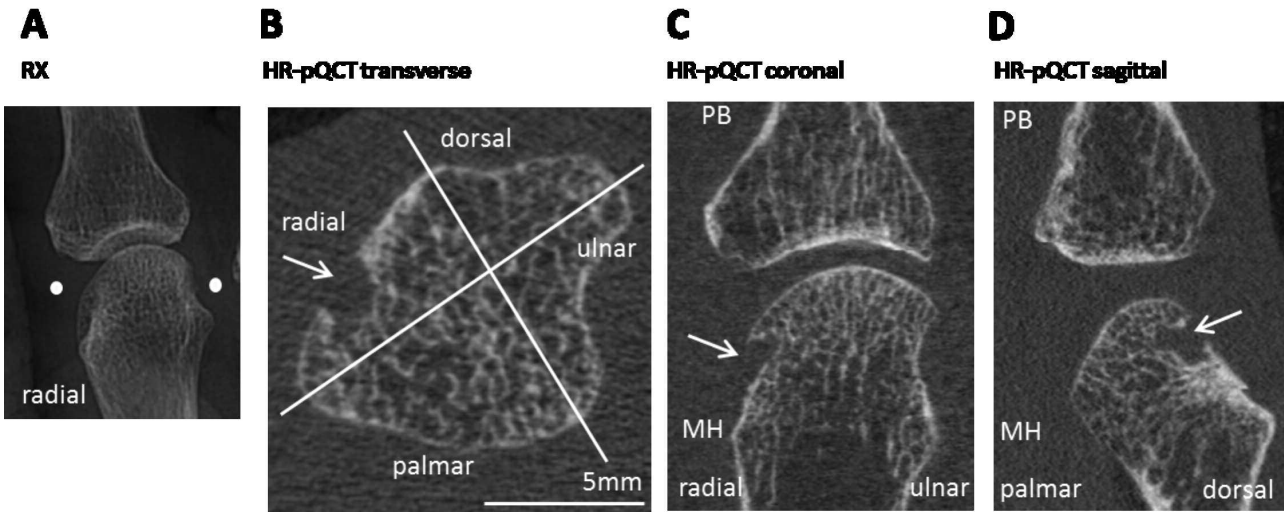


Figure 1. MCP joint on CR (A) and HR-pQCT imaging (B, C, D) of a 62-year-old patient with longstanding RA. The MCP joint is evaluated in transverse view in 4 quadrants (B) and simultaneously viewed in coronal (C) and sagittal (D) planes. A cortical break is seen in the radial quadrant, and in corresponding coronal and sagittal planes. White dots in A correspond to the location of the transverse slice in B. MCP: metacarpophalangeal; CR: conventional radiography; HR-pQCT: high-resolution peripheral quantitative computed tomography; PB: phalangeal base; MH: metacarpal head.

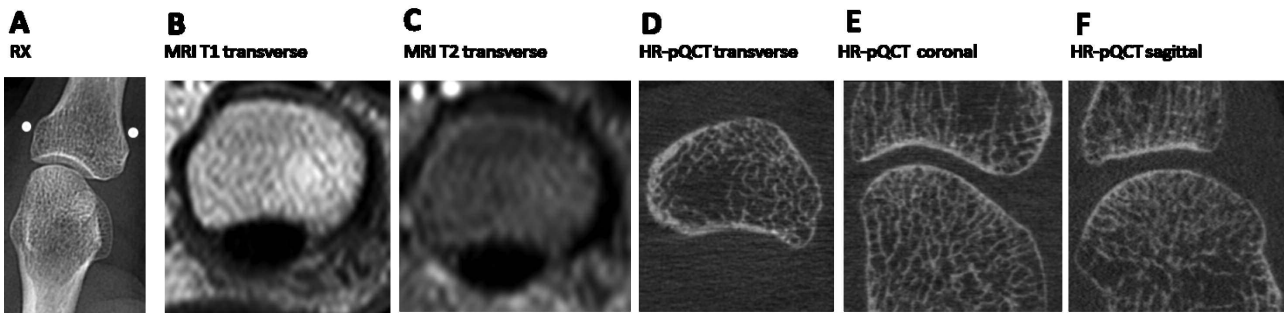
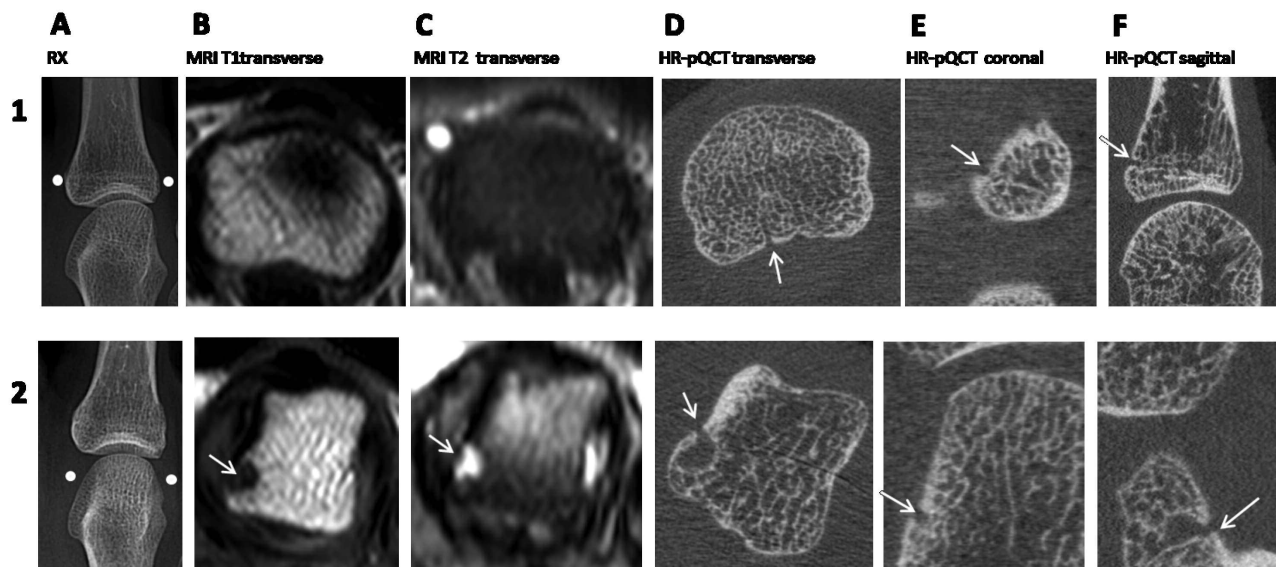
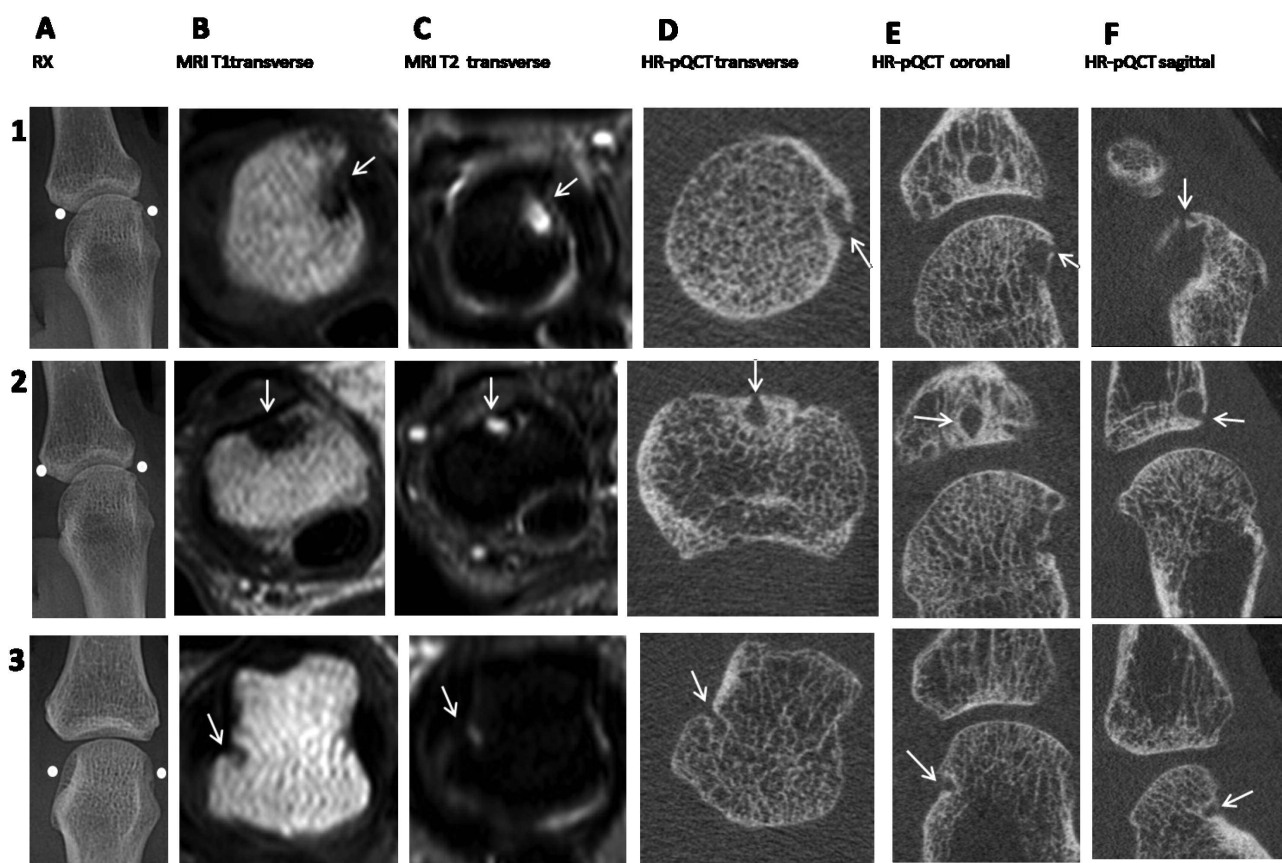


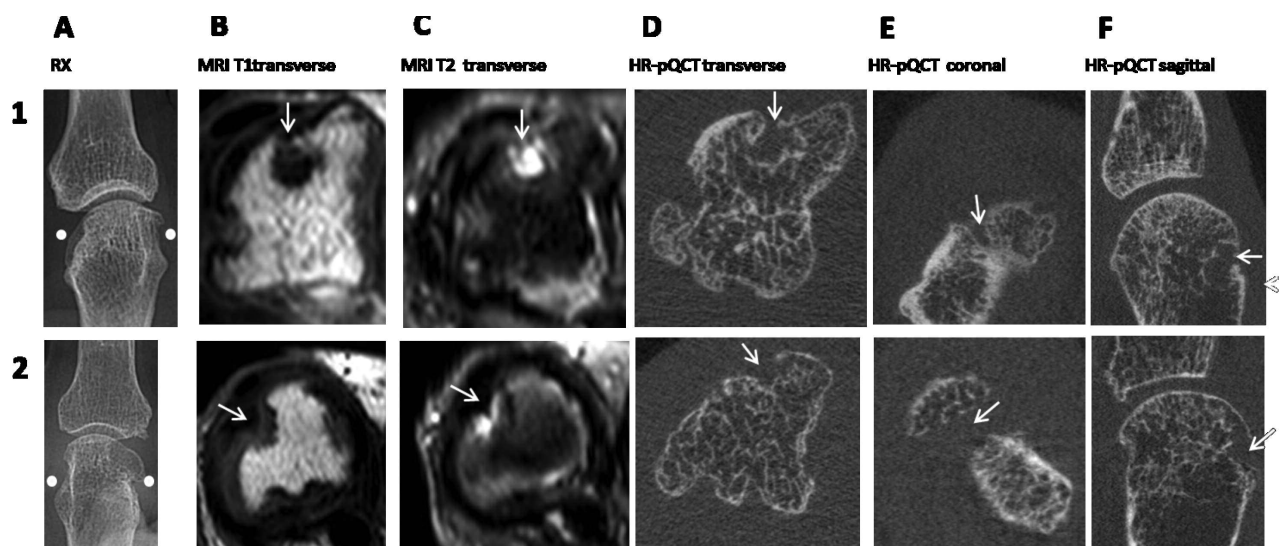
Figure 2. Normal MCP joint on CR (A) and HR-pQCT (D, E, F) of a 61-year-old healthy control. The cortical bone has a smooth outer contour without discontinuities. The normal subcortical trabecular bone shows an evenly distributed branching structure that merges with the cortical bone. The corresponding MRI images (B, C) also show a normal bone without BME and no signs of synovitis. MCP: metacarpophalangeal; CR: conventional radiography; HR-pQCT: high-resolution peripheral quantitative computed tomography; BME: bone marrow edema.



**Figure 3.** Two variants of cortical bone found in MCP joints on CR (A), and HR-pQCT imaging (D, E, F), in transverse, coronal, and sagittal views (D, E, F) in healthy controls (panel 1: age 37 years; panel 2: age 61 years). On panel 1, a cortical break is seen on the palmar side, which is suggestive of a vascular channel with no presence of BME and synovitis on MRI (B, C). Panel 2 shows a subcortical cyst on the radial side without presence of BME and no synovitis on MRI (B, C). White dots on the CR correspond to the location of the cortical break on HR-pQCT imaging. No abnormalities were found on CR. MCP: metacarpophalangeal; CR: conventional radiography; HR-pQCT: high-resolution peripheral quantitative computed tomography; BME: bone marrow edema; MRI: magnetic resonance imaging.



**Figure 4.** No cortical breaks in MCP joints on CR (A) but cortical breaks in MCP joints on MRI (B, C) and HR-pQCT (D, E, F) in patients with early RA (panels 1 and 2: age 59 yrs, panel 3: age 58 yrs). Disease duration of patient in panels 1 and 2: 19 months (RF-/ACPA-); panel 3: 4 months (RF-/ACPA-). BME is seen in panels 1 and 2, but no synovitis on MRI. MCP: metacarpophalangeal; CR: conventional radiography; HR-pQCT: high-resolution peripheral quantitative computed tomography; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; BME: bone marrow edema; MRI: magnetic resonance imaging; RA: rheumatoid arthritis.



**Figure 5.** Cortical breaks in MCP joints on 3 imaging modalities: CR (A), MRI (B, C), and HR-pQCT (D, E, F) in patients with longstanding RA (panel 1: age 55 yrs; panel 2: age 65 yrs). Disease duration of patient in panel 1: 286 months (RF+/ACPA unknown) and panel 2: 166 months (RF-/ACPA-). Panel 1 shows presence of BME and synovitis on MRI. Panel 2 shows no presence of BME but presence of synovitis on MRI. MCP: metacarpophalangeal; CR: conventional radiography; HR-pQCT: high-resolution peripheral quantitative computed tomography; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; BME: bone marrow edema; MRI: magnetic resonance imaging.

patients with early and longstanding RA we selected images of joints with clear cortical breaks (Figures 4 and 5). All images are shown with corresponding radiographs and MRI.

**Healthy controls.** Characteristic for normal cortical bone is its smooth outer contour without cortical breaks, accompanied by normal subchondral trabecular bone with an evenly distributed branching structure that merges with the cortical bone. Figure 2 presents an example of normal cortical bone in an MCP joint of an HC. On CR, no cortical break is visible and on MRI there are no signs of BME or synovitis.

Nevertheless, cortical breaks were also seen in HC. Figure 3 panel 1 shows an example of a cortical break suggestive of a vascular channel, based on the parallel lining of the break and presence of normal trabecular structure (panel 1). This cortical break is not visible on CR or MRI, and there were no signs of BME or synovitis on MRI. Figure 3 panel 2 shows an example of a small cortical break with a large area of trabecular bone loss suggesting a subchondral bone cyst, which is barely visible on CR but clearly found on MRI without presence of BME and synovitis.

**Rheumatoid arthritis.** Figure 4 shows examples of cortical breaks, considered characteristic for bone erosions, in patients with early RA, at the ulnar (panel 1), dorsal (panel 2), and radial (panel 3) sides as visualized on images from HR-pQCT. Erosions are not visible on CR, but can be seen on MRI, with presence of BME in panel 1 and 2 but without synovitis (all panels).

Figure 5 shows 2 examples of patients with longstanding RA with large cortical breaks with irregular surrounding cortical lining and extensive surrounding trabecular bone loss, suggestive of bone erosions. These are also visible on

CR and MRI, with presence of BME and synovitis on MRI in panel 1 and without presence of BME but presence of synovitis in panel 2 (Figure 5).

## DISCUSSION

The HR-pQCT images of MCP joints shown in this image review serve as an illustration of intact cortical bone and heterogeneous cortical breaks found not only in patients with early and longstanding RA, but also in HC.

On HR-pQCT, cortical breaks are found on all sides, i.e., radial, ulnar, palmar, and dorsal; and in both the metacarpal head and the phalangeal base. Breaks vary from very small to very large, and are located close to and/or remote from the joint space. Also, highly variable damage to the trabecular structure in terms of size and delineation (with or without bone sclerosis) is seen. As expected, the presence and size of bone damage is more pronounced and complex on HR-pQCT than can be observed on CR<sup>12,14,19,21,22</sup>.

HR-pQCT is a clinically feasible modality, with radiation exposure levels of < 3  $\mu$ Sv, and scan time of < 9 min for standard scans, a duration most patients can tolerate. The major advantage over CR is its 3-D resolution. CR provides a projection of spatial structures, which may lead to errors in interpretation due to positioning and superimposition. HR-pQCT overcomes this problem, i.e., the examination can be viewed simultaneously in transverse, coronal, and sagittal plane, creating a 3-D impression of the joint. Also, it provides opportunities for measuring new, potentially very relevant characteristics, such as the 3-D joint space volume and cortical break and erosion volume by manual or semiautomatic assessment<sup>18,19</sup>. However, the HR-pQCT also has its

limitations, such as the limited availability of the system, the time presently involved in scoring and interpreting the images, operator-dependent variation when a cortical break is considered an erosion, and movement artefacts, which can reduce accuracy<sup>23</sup>. Further, although scan time of the joints is relatively short, only a few joints are imaged due to the limited field of view of HR-pQCT compared to CR and MRI.

Although characteristic of RA, cortical breaks indicating bone erosions are not specific to the disease; breaks are also found in, for example, psoriatic arthritis, osteoarthritis, and crystal arthropathies. More important, cortical breaks are also found in HC. This represents a challenge regarding the clinical significance and nature of a cortical break as seen on HR-pQCT. While in CR, the terms bone erosion and cortical break are used interchangeably, this should not be the case for cortical breaks seen with HR-pQCT. Indeed, some cortical breaks on HR-pQCT suggest a vascular channel or a bone cyst not related to RA. In HC, cortical breaks can reflect damage as a result of natural bone turnover or a microdamage repair process<sup>24,25</sup>. In addition to cortical erosions, which are full cortical breaks, intracortical bone porosity without erosions can also be found in RA, increasing the complexity of cortical bone changes in RA<sup>26</sup>. SPECTRA developed preliminary definitions for erosions, vascular channels, and subchondral cysts, which need validation. Methods of validation will include comparison with microCT and histology in cadaver fingers.

Similar to the detailed scoring of CR, interpreting bone changes on HR-pQCT will require training<sup>7</sup>. Quantification of these cortical and trabecular bone changes will need new imaging analysis systems. It is highly desirable that a (semi)automatic algorithm be developed in view of the high amount of image slices for increasing feasibility in research and practice. It will be necessary to investigate the relationship between bone changes found on HR-pQCT versus those on other imaging techniques, both cross-sectionally and longitudinally. For example, bone damage in RA reflects a history of events that are driven by inflammatory mechanisms, which can be visualized by MRI and ultrasound (e.g., BME, synovitis, enthesitis, tendinitis, vascularization)<sup>4</sup>. It is of interest to determine whether the bone changes visualized by HR-pQCT follow this inflammatory process, at which locations, and in which order. Finally, it needs to be investigated whether the heterogeneity seen in cortical breaks potentially can be used to better understand the pathophysiology of bone damage, and the predictive value of certain lesions for progression in damage.

SPECTRA will continue to work on refining definitions for cortical breaks and erosions, and develop definitions for other abnormalities found in cortical bone and trabecular bone structures imaged by HR-pQCT. SPECTRA has initiated studies comparing cortical and trabecular bone defects as imaged by HR-pQCT with those of conventional radiology, histology, microCT, MRI, and ultrasound to

validate the HR-pQCT as a tool for measuring outcome in rheumatologic clinical trials. Moreover, SPECTRA aims to provide a substantial methodological basis, using the filters of truth, discrimination, and feasibility as described by the Outcome Measures in Rheumatology (OMERACT) Filters 1.0 and 2.0, for application as an OMERACT Special Interest Group<sup>27</sup>.

This image review demonstrates HR-pQCT images of MCP joints showing the cortical and subchondral trabecular bone structure in HC and the heterogeneous spectrum of cortical breaks in patients with RA. Future studies are needed to validate the HR-pQCT and to investigate its application in research and practice.

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## ONLINE SUPPLEMENT

Supplementary data for this article are available online at [jrheum.org](http://jrheum.org).

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