Introduction

The Role of High-resolution Peripheral Quantitative Computed Tomography as a Biomarker for Joint Damage in Inflammatory Arthritis

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ABSTRACT. Since 2011, members of the SPECTRA Collaboration (Study grouP for xtrEme-Computed Tomography in Rheumatoid Arthritis) have investigated the validity, reliability, and responsiveness of high-resolution peripheral quantitative computed tomography (HR-pQCT) as a biomarker for joint damage in inflammatory arthritis. Presented in this series of articles are a systematic review of HR-pQCT-related findings to date, a review of selected images of cortical and subchondral trabecular bone of metacarpophalangeal (MCP) joints, results of a consensus process to standardize the definition of erosions and their quantification, as well as an examination of the effect of joint flexion on width and volume assessment of the joint space. (J Rheumatol 2016;43:1911–13; doi:10.3899/jrheum.160645)

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Radiographic progression is a key outcome in inflammatory arthritis trials and longitudinal observational studies. However, because plain radiography provides only a 2-dimensional evaluation of a 3-dimensional (3-D) surface, errors may occur related to positioning and to overlapping bony interfaces in particular views. Current radiographic scoring schemes based on ordinal scoring of joint space width and erosions may predispose to floor and ceiling effects. Significant progression is required to reach the incremental worsening threshold to detect score progression[1]. Moreover, with early diagnosis and treat-to-target strategies, patients enrolled nowadays tend to have low levels of damage at baseline, with little progression expected in either the treatment or placebo group, compounded with early timing of rescue therapies and limited exposure duration, all of which greatly limit the power of current radiographic scoring schemes.

Why do we need high-resolution peripheral quantitative computed tomography (HR-pQCT)?

HR-pQCT has introduced a new dimension in the imaging of bone and joints by providing images that are both 3-D and at high resolution (82 μm isotropic voxel size), with a low level of radiation exposure (3–5 μSv). With the high spatial resolution, HR-pQCT allows for detection of periarticular bone damage such as erosions, cysts, joint space narrowing, and bone proliferations in inflammatory and degenerative disease[2,3]. The quantitative nature of the technology allows calculation of periarticular bone mineral density (BMD) and microarchitecture, with excellent reproducibility[4,5,6]. With a higher sensitivity to change, HR-pQCT would be of great use to improve radiographic progression determination in clinical trials and longitudinal observational studies in patients with arthritis. Moreover, it is safe, with a very low irradiation dose; and the scanning protocols are well tolerated by patients with active inflammation. HR-pQCT could improve the detection of pre-erosive bony changes, and provide quantitative measurements of BMD and microarchitecture, which would be of value in clinical trials and complementary to emerging imaging biomarkers.

Since 2011, members of the SPECTRA Collaboration (Study grouP for xtrEme-Computed Tomography in Rheumatoid Arthritis) have investigated the validity, reliability, and responsiveness of HR-pQCT as a biomarker for joint damage in inflammatory arthritis. Our goal is to expand the use of HR-pQCT as an imaging biomarker for diseases affecting the small joints of the hands and wrists.

What has been done so far?

Because the body of literature has grown substantially, the SPECTRA group undertook a systematic review to summarize findings. Nagaraj, *et al* identified 44 studies

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reporting on pathology findings, including erosions, bone microarchitecture, BMD measures, joint space evaluation, or osteophyte characterization[7]. The vast majority of studies identified focus on characterizing erosions. Erosions have been assessed in a variety of arthritis conditions including early inflammatory arthritis, rheumatoid arthritis (RA), psoriatic arthritis, erosive hand osteoarthritis, as well as in persons with psoriasis and healthy controls (HC), and subjects with anticyclic citrullinated antibody antibodies but no features of arthritis. Seventeen of the studies compared HR-pQCT findings to conventional radiography (CR), ultrasound (US), magnetic resonance imaging (MRI), or micro-computed tomography (microCT), with HR-pQCT having high sensitivity for erosion detection. Twenty-four studies included an assessment of reproducibility with good to excellent metrics. In view of its high resolution and increased sensitivity to detect erosion, HR-pQCT has been used in further studies as the gold standard for erosions relative to MRI, power Doppler US, high-resolution US, and plain radiography.

What can be seen?

To show the spectrum of cortical breaks visualized on HR-pQCT, the SPECTRA group has taken another initiative to compile a review of selected images of cortical and subchondral trabecular bone of metacarpophalangeal (MCP) joints of patients with RA and HC, with corresponding images on CR and MRI. The image review by Scharmga, *et al* served as an illustration of intact cortical bone and heterogeneous cortical breaks that are found in patients with early and longstanding RA, but also in HC[8]. They are heterogeneous in size, location, and number per joint, with a variety of surrounding cortical and underlying trabecular bone characteristics. Cortical breaks seen in HC may be suggestive for a vascular channel, based on the parallel lining of the break and presence of normal trabecular structure. Cortical break with a large area of trabecular bone loss may suggest a subchondral bone cyst that is barely visible on CR but clearly found on MRI without presence of bone marrow edema (BME) and synovitis. Cortical breaks characteristic for bone erosions in RA may or may not be associated with BME and synovitis on MRI.

Is HR-pQCT a valid assessment tool for erosion and joint space narrowing in RA?

Early independent work in detecting erosions with HR-pQCT and quantifying their size resulted in multiple definitions and size measurement methods reported in the literature[2,9,10,11,12]. SPECTRA thus prioritized achieving consensus on a definition for erosions, and standardizing reference points for erosion size measurements in 2 dimensions until a 3-D protocol can be validated. A first Reliability Exercise (RELEX-1) was performed to facilitate these objectives[13]. Pathologic erosions were defined as cortical breaks extending over a minimum of 2 consecutive slices in perpendicular planes, with underlying trabecular bone loss and a nonlinear shape. Interreader agreement for classifying pathologic erosions was 90.2%, whereas variability for width and depth erosion assessment was observed. Similar to detailed scoring of CR, training will be necessary to interpret bone changes on HR-pQCT[14].

New methods to determine measurements between bony surfaces of the joint, reflecting joint space width, have been devised[15,16]. The effect of positioning on joint space width measurements has been established, although the optimal positioning angle remains undefined[16]. Tom, *et al* addressed the effect of joint flexion on width and volume assessment of the joint space in a cadaver study[17]. They calculated the variation in joint space width and volume measurements obtained when the degree of flexion at the MCP joints is varied. Acceptable reproducibility values for mean and maximum joint space as well as joint space volume were obtained up to 20° of flexion, while a position of < 10° afforded the optimal value for minimum joint space width determination. Therefore, MCP joint space measurements should be acquired at < 10° of flexion in future longitudinal studies.

What the future holds

The vast majority of studies we identified focus on characterizing erosions, with an apparent evolution in case definition standardization. The SPECTRA group is currently performing a Delphi exercise to confirm consensus of the definition for erosion. Longitudinal erosion assessment has also been done to further test the erosion definition. In RELEX-2, 4 experienced readers (2 with > 5 yrs of experience, 2 with > 3 yrs of experience) read longitudinal datasets for the presence of erosions, and then calculated erosion dimensions. A major limitation of this work is the training required to increase interreader reliability and the time to score images. A key activity moving forward will be to apply semiautomated script algorithms to immediately calculate erosion dimensions. These scripts will be tested in 2 longitudinal studies: the Biologics Healing Study being performed at the University of Calgary, and Erosion Healing and Restoration of Function in Rheumatoid Arthritis. These longitudinal studies will determine the quantitative changes occurring in bone erosions during treatment with biologic therapies.

In addition to cortical erosions that are full cortical breaks, intracortical bone porosity without erosions can also be found in RA, increasing the complexity of cortical bone changes in RA[4]. SPECTRA developed preliminary definitions for erosions, vascular channels, and subchondral cysts, which need validation. Methods of validation will be the comparison with microCT and histology on cadaver fingers. Because the difference between pathological cortical breaks (i.e., erosions) and physiological cortical breaks (i.e., vascular

channels) is currently based on appearance on HR-pQCT images and some preliminary studies using US, confirmation by histology and perfusion studies is ongoing for the validation of the method. Further work should be directed to refining what is a naturally occurring erosive finding and how it becomes pathological. The underlying mechanisms and significance of this spectrum of cortical breaks as found with high 3-D resolution needs further investigation. Some areas of pathology description require further development, such as defining and measuring osteophytes. It is also necessary to achieve consensus on methods for measuring joint space width, along with correlation to tissue studies to confirm findings.

Imaging is essential to the evaluation of bone and joint diseases. HR-pQCT has introduced a new dimension in the imaging of bone and joints by providing images that are both 3-D and at high resolution, with a low level of radiation exposure. HR-pQCT makes possible the *in vivo* assessment of the spatial distribution, dimensions, and delineation of cortical bone erosions, osteophytes, periarticular cortical and trabecular microarchitecture, and 3-D joint space volume of the finger joints and wrists. HR-pQCT is therefore a technique with a high potential for improving our understanding of bone and joint diseases at the microarchitectural level.

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