

Quantification of small joint space width, periarticular bone microstructure and erosions using high-resolution peripheral quantitative computed tomography in rheumatoid arthritis

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Abstract

Objectives

This paper aims to investigate the ability of a novel imaging technique, high-resolution peripheral quantitative computed tomography (HR-pQCT), to quantify joint space width at the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, and provide periarticular bone microstructure measurements (including volumetric density and morphometric indices). We also compared the sensitivity and specificity of HR-pQCT to detect erosions relative to plain radiography.

Methods

HR-pQCT imaging of the MCP and PIP joints of the dominant hand was performed in 30 rheumatoid arthritis (RA) and control subjects matched for age, sex and dominant hand use. The joint space width was calculated by determining the number of voxels between three-dimensional images of the articular surfaces. Periarticular bone microstructure was quantified for the 2nd and 3rd MCP joints using standard analysis. The presence of erosions was confirmed by viewing both two- and three-dimensional images of the joints.

Results

Quantitative measures of joint space width and periarticular bone microstructure were obtained with precision. Although not powered to detect differences between RA and control subjects, we identified a trend to narrowing of the 2nd MCP joints in RA (mean difference 250 μ m, $p=0.057$). RA erosions most frequently occurred at the metacarpal head of the MCP joint, and HR-pQCT identified erosions in 24.7% more joints compared to plain radiography.

Conclusion

This is the first study to exploit the quantitative capabilities of HR-pQCT to provide joint space width measurements at the MCP and PIP joints. We provide further proof that HR-pQCT improves erosion detection and yields reproducible periarticular bone microstructure measurements.

Key words

high-resolution peripheral quantitative computed tomography, rheumatoid arthritis, diagnostic imaging

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Introduction

Significant achievements have occurred in rheumatoid arthritis (RA) management over the last 15 years. There has been substantial interest in using more sensitive imaging tools such as magnetic resonance imaging (MRI) and ultrasound to enable early diagnosis and follow disease progression over time (1-7). These tools are ideal for detecting soft tissue changes such as tenosynovitis and joint effusions, and bone marrow oedema visualised by MRI appears to be the precursor lesion to erosions (8, 9). More recently, the importance of identifying progressive joint space narrowing has been highlighted, as cartilage loss has been associated with greater decline in function over time relative to erosions (10). Unfortunately, the ability of ultrasound and MRI to provide a joint space width measurement is currently limited as these techniques do not afford a precise assessment of cortical bone margins (11).

Computed tomography (CT) imaging has not been adopted in routine RA diagnosis and monitoring, given concerns of accessibility and radiation exposure (12). CT is, however, well suited for imaging bone relative to MRI and ultrasound (13). Cortical bone is densely mineralised, and CT imaging provides clear contrast between bone and soft tissue which is ideal for determining joint and erosion margins (14). CT has multiplanar capabilities, and multidetector technology is superior to MRI and plain radiography in the detection of erosions (13, 15). High-resolution peripheral quantitative computed tomography (HR-pQCT; XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) is an adaptation of CT technology, primarily for metabolic bone research (16). The HR-pQCT instrument is dedicated to imaging of the peripheral limbs, with low radiation exposure (<3µSv per scan (17)). It provides three-dimensional (3D) images with a nominal isotropic resolution of 82 µm, and is able to accurately and reproducibly resolve human bone microarchitecture *in vivo* (18, 19). The primary measurements available from HR-pQCT are volumetric bone density and morphometric indices of

bone microstructure including cortical thickness, trabecular thickness, and the separation and number of trabeculae. The volumetric data is ideal for use by finite element analysis to non-invasively study the biomechanical properties of bone (17, 20).

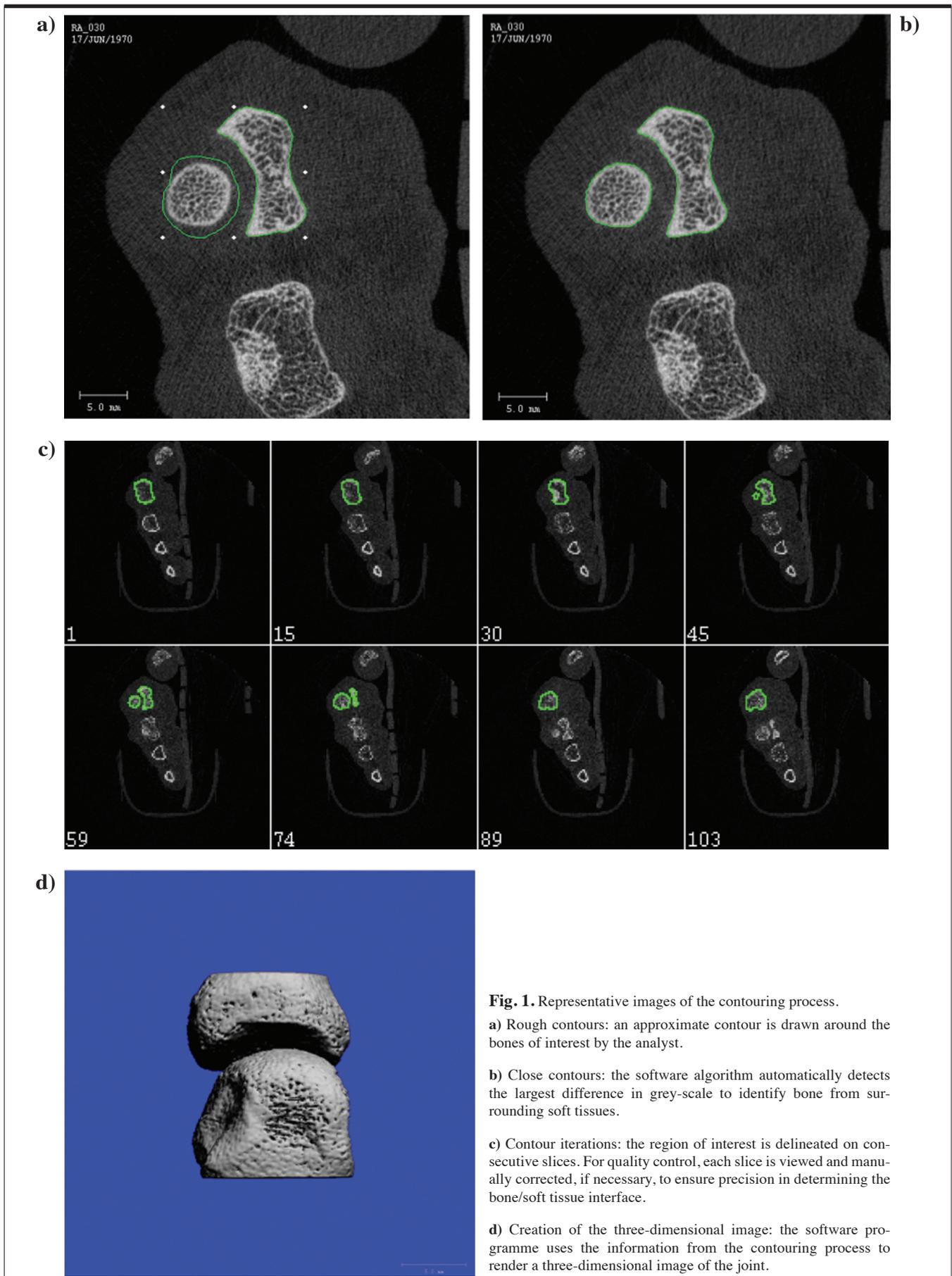
The objective of our study was to determine the feasibility of adapting HR-pQCT technology to study bone structure and damage of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of subjects with RA. We wanted to determine if HR-pQCT could quantify periarticular bone microstructure, and given its ability to detect bone margins, provide a measurement of the joint space width considering the 3D aspect of the joint, in patients with well-characterised disease. We also wanted to compare the sensitivity of HR-pQCT to detect erosive changes relative to standard plain radiographs. The results of this cross-sectional study provide a baseline for new HR-pQCT protocols to assess the adequacy of treatment response in RA.

Methods

Recruitment and inclusion criteria

Fifteen subjects meeting the American College of Rheumatology 1987 Classification Criteria for RA (21) were identified from the practices of rheumatologists affiliated with our centre. Fifteen age- (within 5 years), sex- and dominant-hand- matched control subjects without RA were identified from the same clinical practices or by voluntary response to recruitment posters in order to inform 'normal' findings. Digital plain radiographs of the dominant hand performed within the past year were reviewed by a rheumatologist (CB) to confirm joint space narrowing or erosive changes at either the proximal interphalangeal (PIP) or metacarpophalangeal (MCP) joints for the RA subjects, and normal images in control subjects. Patients with prior surgery of the MCPs or PIPs and pregnant females were excluded. Ethical approval for the study was provided by the Conjoint Health Research Ethics Board of the University of Calgary, and was in compliance with the Declaration of Helsinki.

Competing interests: none declared.



Procedures

A standard stabilisation platform was created to secure the dominant hand with the MCPs and PIPs extended to a flat position (unless prevented by fixed joint angulation) within the immobiliser cast. The 2nd, 3rd and 4th PIP joints (as a group) and the 2nd, 3rd and 4th MCP joints (as a group) were imaged with two stacks (or 220 slices, 1.8 cm), respectively. One stack (110 slices, 0.9 cm) was required to image each of the interphalangeal joint, the 1st MCP, the 5th PIP and 5th MCP joints. The total effective patient radiation exposure was estimated to be 24 μ Sv (equivalent to less than 1/4 of a standard chest radiograph).

Image analysis

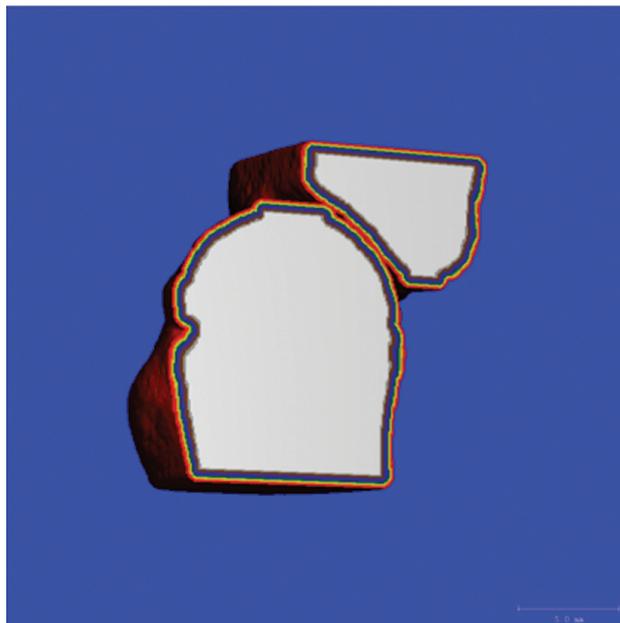
Individual joints were identified in the scan, and a modified automatic contouring algorithm (as developed by Buie *et al.* [22]) was used to identify the periosteal surfaces of both bones comprising the joints of interest (Fig. 1). Quality control was performed for each slice by manual viewing to ensure that the generated contours were accurate and correctly identified the interface, in particular at the joint margin itself. Subsequently, the mineralised tissue was determined using the manufacturer's standard global thresholding technique (17).

We determined the joint space width by region growing analysis performed on the 3D images (Image Processing Language, Scanco Medical, v5.08B) (Fig. 2). A direct thickness measure of the joint space at the narrowest location was defined as the minimum joint space width measurement (23).

To determine the periarticular bone microstructure, a maximum of 60 slices from the articular surfaces of each of the proximal and distal bones comprising a joint was identified for the region of analysis for the 2nd and 3rd MCPs. A fully automated method was applied to detect the endosteal surface (dual-threshold segmentation algorithm) (22). Measurements of interest were the relative bone volume (BV/TV, %); density of the whole bone (BMD, mg HA/cm³), cortical bone and trabecular bone components (Ct.BMD and

Fig. 2. Representation of region growing.

An 82 μ m layer is added to both the distal and proximal bone surfaces comprising the joint for each iteration. These layers are added sequentially until one solid object is detected by the software programme.



Tb.BMD, respectively, mg HA/cm³); average cortical thickness (Ct.Th, mm); and trabecular number (Tb.N, 1/mm), separation (Tb.Sp, mm) and thickness (Tb.Th, mm).

Erosions were defined as a definite cortical break on a two-dimensional image extending over a minimum of three 82 μ m slices. All three orthogonal planes (coronal, longitudinal and transverse) were viewed to confirm the presence of an erosion. The number of individual erosions and their location were recorded.

Image quality was scored using a semi-quantitative scale and only acceptable images (Grades 1 to 3), as suggested by the manufacturer, were included in our analysis. The reproducibility of the contouring algorithm and determination of erosions was assessed by recontouring and rescoring 30 of the 300 randomly selected images blinded to results of the first analysis, and performed at least one month later. This study did not specifically address the reproducibility of repeat positioning and scanning, as previous work in our laboratory demonstrated that repositioning errors at the standard sites for microstructure analysis (the distal radius and distal tibia) in osteoporosis studies account for less than 1.5% of the variability in measurements (18), and as patients were already undergoing approximately 20 minutes of scanning.

Comparison of HR-pQCT performance to plain radiography and clinical diagnosis

Plain radiographs were scored for erosions by two experienced rheumatologists using the van der Heijde modification of the Sharp score (vdHSS) (24). The scores were then transformed to a binary determination of the presence of erosions (*i.e.* present or absent). We calculated the probability of agreement between plain radiography and HR-pQCT for erosion determination at each joint.

Statistical analysis

Patient demographics were summarised as means or proportions as appropriate. Mean joint space width and periarticular bone microstructure measures for RA subjects and controls were compared within ten matched sets defined by an individual's age, sex and dominant-hand, with the mean difference of all sets presented. Comparison of the two subject groups was performed using the Student's *t*-test for parametric results (joint space width) and Wilcoxon signed-rank test for non-parametric results (periarticular microstructure), although the study was not powered for statistical significance *a priori*. The mean number of erosions in RA subjects and controls was calculated, with reporting of their location by joint and bone surface. The reproducibility of

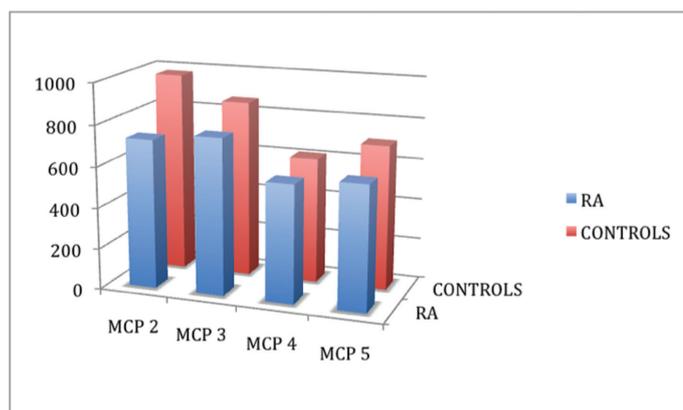


Fig. 3a. Mean joint space width of the metacarpophalangeal (MCP) joints (μm).

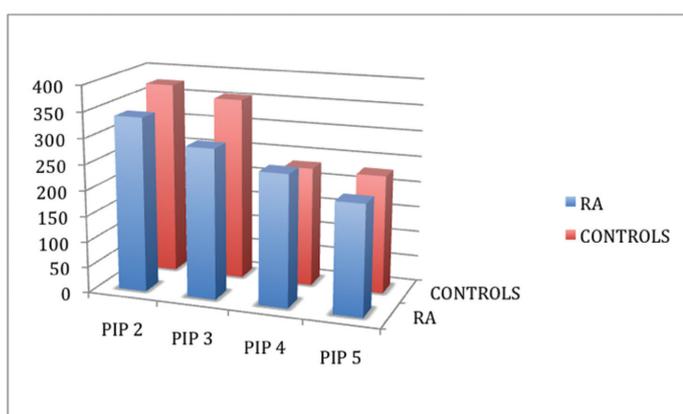


Fig. 3b. Mean joint space width of the proximal interphalangeal (PIP) joints (μm).

joint space width and periarticular bone microstructure measurements was assessed using the root mean square coefficient of variance (25).

Results

Patient demographics and scan quality for inclusion in the analysis

The mean age of the RA subjects was 46.4 years (standard deviation, [SD] 15.9), 87% were female, and 93% were

right hand dominant. The average disease duration was 10.6 years (SD 11.7, range 1.5–46 years) and 67% were rheumatoid factor positive. All patients had been treated with hydroxychloroquine, all but one had been treated with methotrexate, and 40% were on biologic therapies. We had to exclude 47 of the 300 joints imaged (15.7%) from joint space width and periarticular microstructure analysis due to poor image quality (*e.g.*

movement artifact) or due to positioning errors (*e.g.* thumb joints that had been positioned too close to the edge of the detection field). For erosion analysis, 17 of the 300 joints imaged (5.7%) were excluded due to poor image quality.

Joint space width

Using region growing image processing, we were able to ascertain joint space width for all subjects at the 2nd through 5th MCP and PIP joints. RA subjects had narrowed MCP joints compared to their matched controls at all joints, except the 4th PIP joint (Fig. 3). Despite this pilot study not being powered to detect significant differences in joint space width between RA subjects and controls, we identified a trend to significant narrowing in RA subjects at the 2nd MCP joint (mean set difference 250 μm [standard deviation, SD 282], paired *t*-test $p=0.0572$).

Periarticular bone microstructure

Measures of periarticular bone density and microarchitecture were obtained for a 120 slice region of the 2nd and 3rd MCP joints (Table I). In general, RA subjects had a higher mean bone volume/total volume ratio and a higher whole bone density than control subjects. There was a trend for RA subjects to have a higher trabecular bone density, with a higher average trabecular number and trabecular thickness. Cortical thickness was reduced for RA subjects, however, cortical bone density was similar for both groups.

Table I. Morphometric indices.

	2 nd Metacarpophalangeal joint mean (SD)			3 rd Metacarpophalangeal joint mean (SD)		
	RA	Control	Mean set difference*	RA	Control	Mean set difference*
Bone volume/total volume ratio, %	.477 (.061)	.440 (.031)	-.037 (.077)	.455 (.025)	.429 (.036)	-.026 (.058)
Whole bone density, mg/cm^3	403.37 (57.57)	383.91 (31.73)	-19.46 (71.54)	379.35 (31.14)	359.10 (34.39)	-20.25 (63.46)
Average cortical thickness, mm	.328 (.040)	.335 (.031)	.006 (.044)	.310 (.031)	.304 (.023)	-.006 (.046)
Cortical density, mg/cm^3	647.12 (42.77)	661.37 (27.81)	14.25 (51.40)	639.28 (45.05)	632.97 (28.67)	-6.31 (68.72)
Average trabecular number, mm^{-1}	2.44 (.15)	2.31 (.15)	-.12 (.19)	2.40 (.15)	2.36 (.11)	-.04 (.20)
Average trabecular thickness, mm	.284 (.034)	.273 (.006)	-.011 (.035)	.263 (.014)	.261 (.006)	-.003 (.018)
Average trabecular separation, mm	.338 (.032)	.367 (.032)	.029 (.047)	.347 (.026)	.359 (.027)	.012 (.045)
Trabecular density, mg/cm^3	519.46 (49.54)	508.79 (13.82)	-10.67 (54.75)	508.95 (22.94)	499.12 (21.48)	-9.83 (40.44)

SD: standard deviation; mg/cm^3 : milligrammes of hydroxyapatite per cubic centimetre; mm: millimetre.

*Mean difference between matched subjects calculated as: (control subject value – RA subject value); a negative result indicates that the control subjects had a lower value for that parameter relative to the RA subjects.

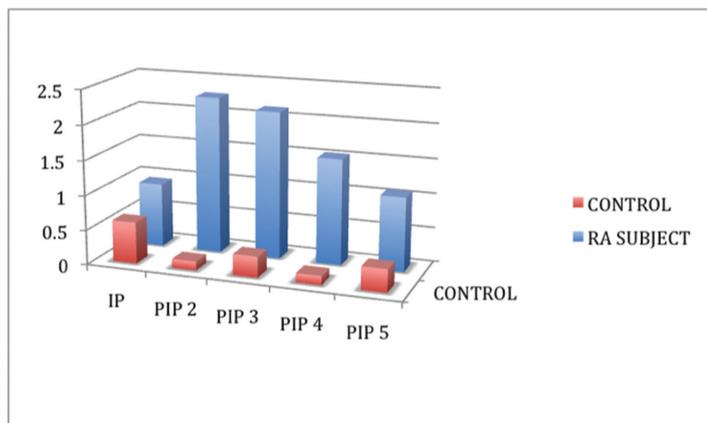
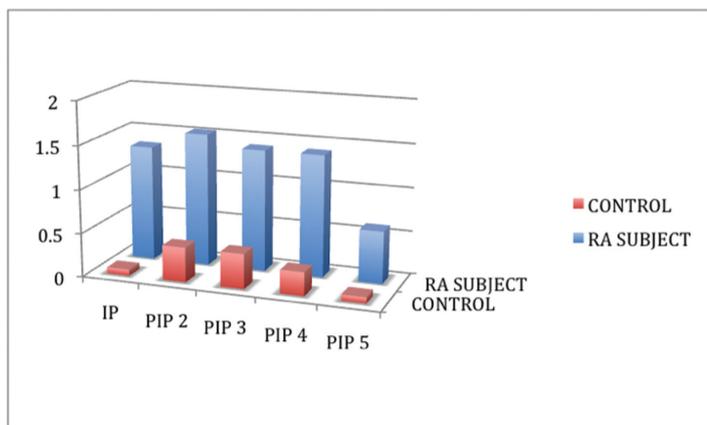
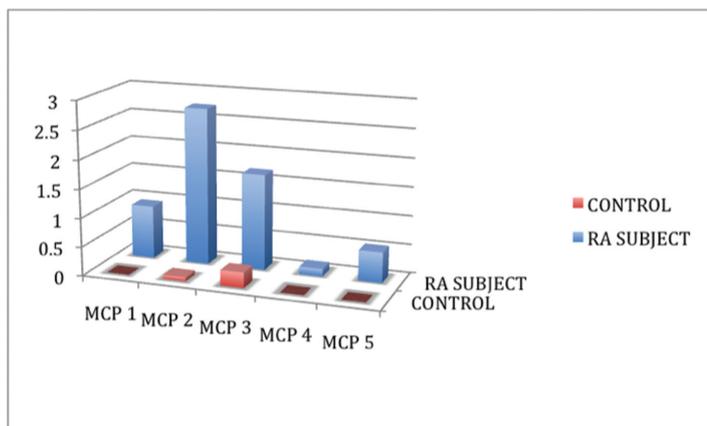


Fig. 4. Mean erosion count for rheumatoid arthritis subjects and controls, by bone surface and joint.

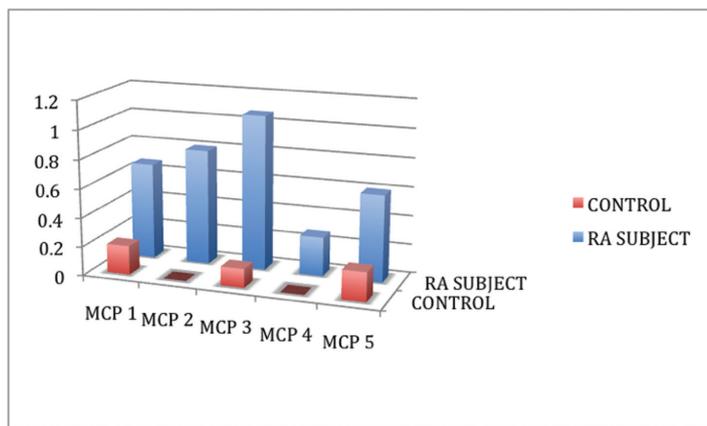
a) Erosions at the proximal phalanx head, PIP joint, mean.



b) Erosions at the middle phalanx base, PIP joint, mean.



c) Erosions at the metacarpal head, MCP joint, mean.



d) Erosions at the proximal phalanx base, MCP joint, mean.

Erosions

Erosions were found in all RA subjects by HR-pQCT, with an average of 23.6 (SD 17.5) erosions over the ten joints imaged. Nine control subjects were also found to have erosions, with a mean erosion count of 3.6 (SD 5.2). Most erosions in RA subjects occurred at the metacarpal head, whereas erosions in control subjects were located at PIP joints (Fig. 4). Vascular channels, which appear as small defects in the cortical bone, extending linearly to the trabeculae, were also recognised.

Comparison of HR-pQCT erosion determination and plain radiography

The probability of agreement between HR-pQCT and plain radiography was 67.5% (n=191/283). Additional erosions, not seen by plain radiography, were visible by HR-pQCT in 70 joints (24.7%). Due to limited scanning of the 4th MCP joint in our HR-pQCT protocol, erosions seen by plain radiography were not detected by HR-pQCT at that joint only.

Contouring reproducibility

The root square mean coefficient of variance for periarticular volumetric bone densities and morphometric indices was excellent, with all values less than 0.83%. The root square mean coefficient of variance for joint space width was higher at 17.1%.

Discussion

This study is the first to develop an imaging protocol to quantify joint space width measurements with 82 µm precision with the hand in anatomical position. The importance of identifying progressive joint narrowing is particularly relevant considering the recent evidence linking joint space narrowing from cartilage loss with declining function over time (10). Additionally, using HR-pQCT to evaluate joint space width is likely superior to the current joint space width determinations attempted with plain radiography and DXR, as the 3D aspect of the joint is taken into account, rather than relying on 2D projection images.

A trend to significant narrowing at the 2nd MCP joint in RA subjects was apparent. Longitudinal assessment is

needed to determine the natural history of joint space narrowing in disease and health states, as well as the impact of treatment on these measurements. The impact of positioning and acute inflammation on joint space width also needs to be studied. Ideally, this work should be performed in conjunction with an imaging technique well suited to image soft tissues, such as ultrasound or MRI. Further assessment of the impact of limitations for determining joint space width, such as image quality, fixed flexion deformities and subluxation, are needed. Reproducibility may be affected by differences in positioning with longitudinal studies, and additional research is required to determine the optimal method to image the joint consistently over time requires further study.

Our study supports the work done by other investigators to assess erosions and periarticular bone microstructure using HR-pQCT in RA. Erosions are recognised as an important feature in RA diagnosis and prognosis. As reported by others, the number, size and site of erosions can be determined with HR-pQCT technology (26-28). In our study, the majority of erosions in RA subjects were localised to the metacarpal head of the MCP joints, with an average of 24 erosions over ten joints per subject in those with established disease. In contrast, erosive changes scored in the control subjects were predominantly at the PIP joints.

Similarly, Stach *et al.* determined that the majority of erosive changes in RA subjects occurred at the radial aspect of the metacarpal head, with an erosion depth of >1.9 mm being specific to those with RA (27). Fouque-Aubert *et al.* did not describe the location of erosions, but rather provided volume estimates (26). Analysis of erosion depth or volume was not pursued in our study, given that we did not have baseline images for the patients and we would have had to impute where the original periosteal surface may have been. The validity of erosion volume estimates remains controversial.

Finzel *et al.* have explored the characteristics of erosions related to particular types of arthritis (28), and also demon-

strated features of normal bony findings such as blood vessel channels, which may be confused as erosive changes using other imaging techniques (29). The evidence that the shape and location of erosions are specific to different types of arthritis is strong. We also found that RA erosions were U-shaped, and that findings of damage such as corticated cysts were common in control subjects, likely reflecting osteoarthritis damage in our subjects.

Fouque-Aubert *et al.* found differences in parameters of bone morphometric indices in RA subjects relative to healthy subjects, accounting for age, which is helpful in further understanding the chronic effects of joint damage (26). It is noteworthy that this group did not identify differences in morphometric indices based on disease duration, which will require further study. There are several possible explanations why our study did not detect measurable differences in trabecular and cortical measurements between RA and control subjects. The first is that this study was not powered to detect small differences between groups. For example, 50 patients in each subject arm would be required to detect a 5% difference in trabecular bone density such as that described in the study of Fouque-Aubert *et al.* (26), with a power of 90% and a one-tailed 5% level of significance. In addition, a larger area of analysis may be required to detect all relevant changes in periarticular bone. Furthermore, we included patients with established disease on stable treatments, without significant clinical inflammation, but with secondary degenerative changes such as sclerosis, cystic change and large erosions, all potentially affecting density measurements. Finally, measurements in both subject groups were not corrected for confounding factors of systemic osteopenia or osteoporosis, nor disease activity levels over time, given the cross-sectional nature of the study.

The other methods described for assessing periarticular bone changes, dual energy x-ray absorptiometry (DEXA) and digital x-ray radiogrammetry (DXR) (summarised in Pfeil *et al.*), use the mid metacarpal shaft as the region of interest for measurement of bone mineral

density, cortical thickness, metacarpal bone width, metacarpal index (ratio of cortical thickness to total bone width) and porosity index (30). Measurements at that site are sensitive to change with treatment, and were found to correlate with functional status, disease activity parameters and erosive changes. Indeed, future work should compare the results obtained with HR-pQCT and DXR measurements. If these methods are reliably correlated, it would be preferable to use HR-pQCT as it also provides measures of trabecular bone, with the benefit of 3D viewing for other characteristic bony changes of RA.

Owing to superior resolution and 3D viewing capabilities, more erosions are found by HR-pQCT relative to plain radiography. We found erosions in 24.7% more joints, whereas Stach *et al.* found that 58% of the patients with normal radiographs had detectable erosions by HR-pQCT (27). As well, Fouque-Aubert *et al.* found that 7 of 36 early RA patients had erosions of the 2nd MCP by HR-pQCT, and 6 of 36 of the 3rd MCP, despite normal radiographs (26). In patients with established RA, an additional 4 of 14 patients had erosions detected at the 2nd MCP, and 6 of 12 at the 3rd MCP (26).

Conclusion

In summary, we propose methodology for quantifying joint space width in RA, an important consideration for functional outcomes. We have exploited the quantitative capabilities of HR-pQCT in measuring periarticular bone microstructure, considering confounding factors of age, sex, and dominant hand use, which could provide important prognostic information in those with active inflammatory disease. We provide further data on the sensitivity of HR-pQCT to determine erosions relative to plain radiography. HR-pQCT is currently a research tool, limited in its availability for use, but certainly of increasing interest to clinical researchers (31). Although it does not evaluate soft-tissue findings of synovitis and tendonitis, it does provide a non-invasive approach to automatically quantify measures of bone damage, not currently possible with x-ray, MRI and ultrasound. We are committed

to continuing to improve the reproducibility of joint space width measurements and optimising techniques for immobilisation and standardisation, as HR-pQCT imaging shows great promise in its potential to measure bone damage parameters in RA.

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