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FULL PAPER

Cartilage quantification using contrast-enhanced MRI in the wrist of rheumatoid arthritis: cartilage loss is associated with bone marrow edema

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Objective: To quantify wrist cartilage using contrast MRI and compare with the extent of adjacent synovitis and bone marrow edema (BME) in patients with rheumatoid arthritis (RA).

Methods: 18 patients with RA underwent post-contrast fat-suppressed T_1 weighted coronal imaging. Cartilage area at the centre of the scaphoid-capitate and radius-scaphoid joints was measured by in-house developed software. We defined cartilage as the pixels with signal intensity between two thresholds (lower: 0.4, 0.5 and 0.6 times the muscle signal, upper: 0.9, 1.0, 1.1, 1.2 and 1.3 times the muscle signal). We investigated the association of cartilage loss with synovitis and BME score derived from RA MRI scoring system.

Results: Cartilage area was correlated with BME score when thresholds were adequately set with lower threshold at 0.6 times the muscle signal and upper threshold at 1.2 times the muscle signal for both SC (r_s=−0.469, $p < 0.05$) and RS (r_s= −0.486, $p < 0.05$) joints, while it showed no significant correlation with synovitis score at any thresholds.

Conclusion: Our software can accurately quantify cartilage in the wrist and BME associated with cartilage loss in patients with RA.

Advances in knowledge: Our software can quantify cartilage using conventional MR images of the wrist. BME is associated with cartilage loss in RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which causes synovitis, bone marrow edema (BME), bone erosion and cartilage destruction.[1,2] The progression of structural damage in RA is associated with the development of joint deformity and eventually with disability.[3] Aletaha et al demonstrated that cartilage damage appears to be more clearly associated with irreversible physical disability than bone damage.[4] The progression of cartilage destruction should therefore be detected at an early stage and therapeutic interference with cartilage destruction performed. It is generally accepted that the outcome measures in rheumatology RA MRI scoring system (RAMRIS) is currently the gold standard for assessing synovitis, BME and bone erosion.[5] When RAMRIS was initially developed, it was not possible to evaluate thin cartilage layers of the wrist because MRI systems were not sophisticated and it was too unreliable to be included in the score.[6] In recent years, however, improvements in MRI technology have facilitated the assessment of progressive cartilage loss not only in large joints such as the knee, but also in wrist joints.[7–9]

The visual MRI cartilage scoring system of the wrist in RA was reported as a semi-quantitative method.[10] Using this method, McQueen et al indicated that MRI cartilage damage progression is preceded by osteitis and synovitis in RA patients, which included early and established RA, compared to controls.[9] To the best of our knowledge, there are no papers which compare quantitative evaluation of cartilage volume with inflammatory changes using conventional MR sequences in patients with RA.

Kamishima et al quantified pannus volume using short tau inversion recovery (STIR) and contrast MRI of the wrist

Table 1. Clinical and laboratory characteristics of patients with RA

Characteristic	Value
Total no. of subjects included	18
Age, mean (range) years	62 (33–81)
Sex, female/male	11/7
RF positive, yes/no	16/2
Duration of symptoms, median (IQR) months, $n = 16$	20 (8.5–27.5)
ESR, median (IQR) mm h^{-1}, $n = 18$	34 (20.8–75.8)
CRP, median (IQR) mg dl^{-1}, $n = 18$	0.3 (0.1–2.2)
DAS-ESR, mean (SD), n =18	5.1 (1.5)
DAS-CRP, mean (SD), $n = 7$	3.9 (2.1)
RF, median (IQR) , $n = 14$	42.9 (16.6–136.5)
CCP, median (IQR) IU ml^{-1}, $n = 18$	11.9 (0.5–343.0)
MMP3, median (IQR) ng ml^{-1}, $n = 18$	106 (27.8–146)
Prior use of DMARDs, yes/no	10/8
DMARDs, no	
None	8
Methotrexate	3
Tocilizumab	2
Combine therapy	5

CRP, C-reactive protein; CCP, cyclic citrullinated peptide; DMARDs, disease-modifying antirheumatic drugs; DAS, disease activity score; ESR, erythrocyte sedimentation rate; IQR, interquartile range; MMP3, Matrix Metalloproteinase-3; RF, rhematoid factor; SD, standard deviation.

by introducing the adductor pollicis muscle signal intensity (MSI) for optimized thresholding.[11] We hypothesized that cartilage can be quantified by applying dual thresholds in contrast MRI, because cartilage is visualized as an intermediate signal intensity, between the high signal of pannus and the low signal of bony structures. The purpose of this study is to quantify wrist cartilage using contrast MRI and compare that with the extent of adjacent synovitis and BME in patients with RA.

METHODS AND MATERIALS

Patients

18 patients (11 females and 7 males, mean age (range) 62 (33–81) years) with RA participated in this study. Out of 18 patients, 13 patients underwent radiography and MRI of the hand with an average (range) of 9 (0–39) days interval. All patients were diagnosed with RA according to the 2010 American College of Rheumatology/European League against rheumatism classification criteria.[12] This study protocol underwent institutional board review and received ethical approval, and all patients provided informed consent to participate in the study. Clinical and laboratory characteristics of patients with RA are shown in Table 1.

Image acquisition

Radiographs

All plain radiographs of the hand of the postero-anterior view were acquired using digital X-ray equipment (KXO-30R, Toshiba, Tochigi, Japan) under the following standardized conditions: tube voltage 50 kV, tube current 100 mA, exposure 0.05 s, film focus distance 100 cm. The X-ray beam was centred on the centre of the film. The position of the hand was aligned with the pattern on the film to improve reproducibility.

MRI scans

MR images were acquired with a 3.0 T system (MAGNETOM Spectra, SIEMENS, Erlangen, Germany) by using a Hand/Wrist 16 A 3T Tim Coil. Patients were placed in the supine position with arms resting on the side of the body. We examined the dominant hand because images with high special resolution were needed for cartilage volumetry. The following images were obtained for the hand: STIR coronal (TR/TE 4300/71 ms, FOV 220 × 220 mm^2, matrix 320 × 320, 19 slices, slice thickness 2 mm, gap 0.4 mm, NEX 1); pre-contrast T_1 weighted coronal (TR/TE 550/11 ms, FOV 220 × 220 mm^2, matrix 448 × 448, 19 slices, slice thickness 2 mm, gap 0.4 mm, NEX 1); post-contrast fat-suppressed T_1 weighted coronal (TR/TE 582/10 ms, FOV 220 × 220 mm^2, matrix 320 × 320, 19 slices, slice thickness 2 mm, gap 0.4 mm, NEX 2). A bolus of contrast agent [15 ml gadopentetate dimeglumine, Gd-DTPA (Magnevist; Bayer Schering Pharma, Osaka, Japan)] followed by saline chase was manually administered taking 30 s before post-contrast T_1 weighted coronal images were scanned. Images after contrast administration are indispensable as omitting intravenous contrast injection does not change scores of bone erosions and bone edema, but decreases the reliability of synovitis scores.[13]

Visual assessments

Joint space width

Each radiograph was scored using the Sharp/van der Heijde (SvdH) method for joint space narrowing (JSN) by one radiologist

Figure 1. ROI placement for muscle signal measurement. An approximately 100 mm^2 ROI was placed in the adductor pollicis muscle on post-contrast fat-suppressed T_1 weighted coronal images of the hand. ROI, region of interest.

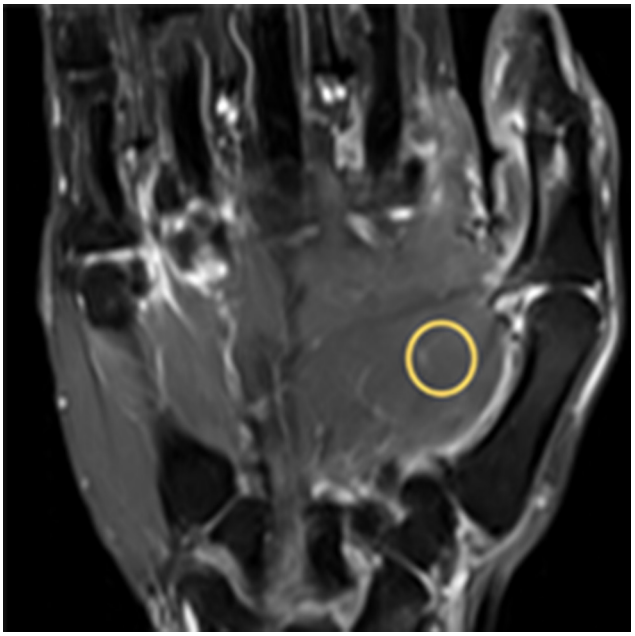
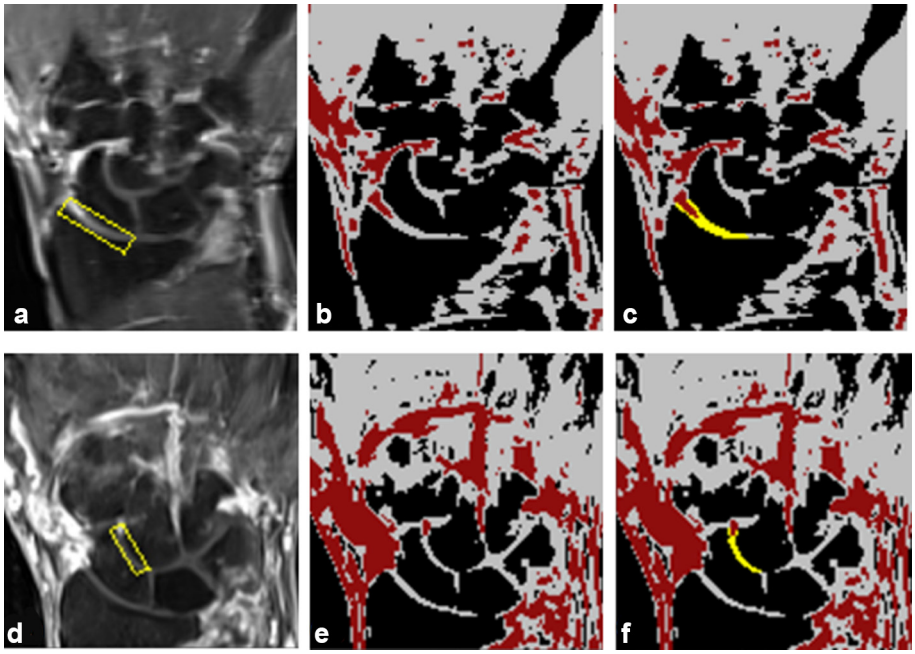


Figure 2. Quantitative measurement of cartilage by in-house developed software. (a), (d) A rectangular ROI placement sized for joint space width of each patient. (b), (e) The whole MR image segmented into three regions; bone (black), cartilage (grey) and synovitis, BME and synovial fluid (red), using two thresholds (T_{lower}-T_{upper}). (c), (f) Calculated cartilage area inside the ROI (yellow). (a), (b), (c) RS joint. (d), (e), (f) SC joint. BME, bone marrow edema; ROI, region of interest; RS, radius-scaphoid joint; SC, scaphoid-capitate joint.



(blinded) with 20 years of experience who was blinded to other clinical information. In this study, JSN for scaphoid-capitate (SC) and radius-scaphoid (RS) joints in the wrist was graded as follows: score 0 = normal; score 1 = focal or doubtful; score 2 =>50% of the original joint space; score 3 =<50% of the original joint space or subluxation; and score 4 = ankylosis or complete luxation.[14]

Synovitis, BME

The same radiologist (blinded) who performed the radiograph analysis scored synovitis at the SC and RS joints using the RAMRIS system on post-contrast fat-suppressed T_1 weighted coronal images as follows: score 0 is normal, and 1–3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. STIR images were evaluated for BME at the joints using the RAMRIS system by the radiologist as follows; score 0 = no edema; score 1 = 1–33% of bone edematous; score 2 = 34–66% of bone edematous; score 3 = 67–100%. Each bone was scored separately.[5,15]

Quantitative measurement of cartilage area

On post-contrast fat-suppressed T_1 weighted images, joint pathologies and normal structures of the wrist can be stratified by relative signal intensity to normal muscle as follows: high signal intensity to normal muscle; synovitis, BME and synovial fluid (synovial fluid is visualized as high signal intensity due to diffusion of contrast agent), low signal intensity to normal muscle;

Table 2. Descriptive statistics of SvdH and RAMRIS scores

	Mean	SD	Median	Range
SvdH scores				
SC	0.38	0.21	0	0–2
RS	0.08	0.08	0	0–1
RAMRIS synovitis				
SC	1.67	0.27	1.5	0–3
RS	1.94	0.24	2	0–3
RAMRIS BME				
SC	0.72	0.32	0	0–5
RS	0.44	0.22	0	0–3

RAMRIS, RA MRI scoring system; RS, radius-scaphoid joint; SC, scaphoid-capitate joint; SvdH, Sharp/van der Heijde score.

Table 3. Cartilage area for each pair of thresholds measured by our software

Joint	T_{lower}-T_{upper} (×MSI)	Mean (mm²)	SD (mm²)	Median (mm²)	Range
SC	0.4_0.9	19.63	1.47	18.91	12.76–35.92
	0.4_1.0	20.60	1.47	19.85	13.71–36.39
	0.4_1.1	21.19	1.41	19.85	15.13–36.39
	0.4_1.2	21.71	1.39	20.32	15.13–36.87
	0.4_1.3	22.02	1.38	20.32	16.07–37.34
	0.5_0.9	15.38	1.32	13.71	9.45–27.41
	0.5_1.0	16.43	1.33	14.65	10.87–27.89
	0.5_1.1	16.96	1.32	14.65	10.87–28.36
	0.5_1.2	17.46	1.29	15.13	12.29–28.36
	0.5_1.3	17.74	1.29	15.60	12.29–28.83
	0.6_0.9	10.82	1.09	9.45	4.73–20.80
	0.6_1.0	11.82	1.14	10.63	5.20–21.27
	0.6_1.1	12.32	1.15	11.58	5.67–21.74
	0.6_1.2	12.81	1.15	11.58	6.14–21.74
	0.6_1.3	13.10	1.14	12.29	6.14–22.21
RS	0.4_0.9	27.86	2.39	22.69	17.96–51.52
	0.4_1.0	30.06	2.31	25.52	21.27–52.46
	0.4_1.1	31.75	2.32	27.89	23.16–53.41
	0.4_1.2	33.06	2.29	29.30	23.63–53.41
	0.4_1.3	33.98	2.32	30.72	24.11–54.36
	0.5_0.9	20.69	1.65	17.49	13.71–34.98
	0.5_1.0	22.95	1.64	20.80	14.18–35.92
	0.5_1.1	24.55	1.73	22.69	16.07–41.59
	0.5_1.2	25.79	1.76	23.63	16.54–43.48
	0.5_1.3	26.65	1.83	24.81	17.02–46.32
	0.6_0.9	15.49	1.45	13.71	7.09–29.78
	0.6_1.0	17.75	1.52	15.13	7.56–30.72
	0.6_1.1	19.35	1.69	17.96	9.45–37.34
	0.6_1.2	20.67	1.75	20.09	9.93–39.23
	0.6_1.3	21.37	1.81	20.56	10.40–42.07

MSI, adductor pollicis muscle signal intensity; RS, radius-scaphoid joint; SC, scaphoid-capitate joint; T_{lower}, lower threshold; T_{upper}, upper threshold.

bone, similar signal intensity to normal muscle; cartilage. We therefore attempted to segment cartilage by the ternarization method with dual thresholds using the adductor pollicis MSI.

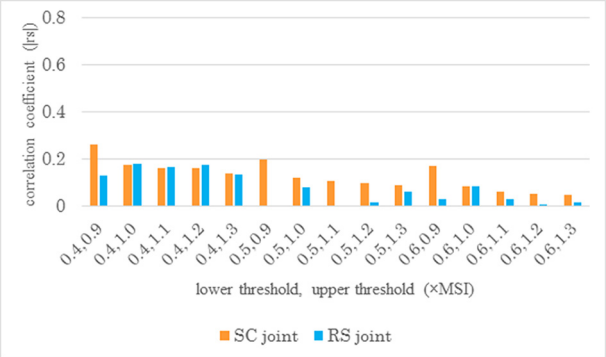
Measurement of adductor pollicis muscle signal intensity

Using the image-processing viewer system EV Insite (PSP Corporation, Tokyo, Japan), we set a region of interest (ROI) of 100 mm² in the adductor pollicis muscle on post-contrast fat-suppressed T_1 weighted images (Figure 1), and calculated the average MSI within the ROI. The slice used for setting the ROI was selected such that the adductor pollicis muscle appeared to reach its maximum size.

Quantitative measurement of cartilage by in-house developed software

The cartilage area of SC and RS joints in the centre of the joint on post-contrast fat-suppressed T_1 weighted images was measured by in-house developed software. If the ROI included signals without cartilage visually in the centre of the joint, we used the adjacent slice. We set 0.4, 0.5 and 0.6 times the muscle signal as a lower threshold (T_{lower}) and 0.9, 1.0, 1.1, 1.2 and 1.3 times the

Figure 3. Correlation between cartilage area and adjacent RAMRIS synovitis. MSI, adductor pollicis muscle signal intensity; SC, scaphoid-capitate joint; RS, radius-scaphoid joint.



muscle signal as an upper threshold (T_{upper}). We defined cartilage area as the pixels with signal intensity between the thresholds. The measurement procedures were performed as follows. The rectangular ROI sized for joint space width of each patient was located manually in the centre of the joint space with attention so that the edges of bones forming the joint were placed inside the ROI (Figure 2a,d). The MR images were segmented into three regions using two thresholds (T_{lower}–T_{upper}) (Figure 2b,e). The cartilage area inside the ROI was then calculated (Figure 2c,f). Measurement of the cartilage area by our software was repeated twice with a period of 1 month.

Statistical analysis

SPSS version 22.0 (IBM Corp., New York, NY) for Windows was performed for the statistical analysis. Intraobserver reproducibility for measurement of cartilage area was estimated using calculations of intraclass correlation coefficient (ICC). Spearman's rank correlation test was used to compare joint space width and cartilage area with RAMRIS synovitis and BME scoring at SC and RS joints. Spearman's correlation coefficient was interpreted as follows: r_s<0.2, poor correlation; r_s=0.2–0.4, fair correlation; r_s=0.41–0.6, moderate correlation; r_s=0.61–0.8, good correlation and r_s>0.81, excellent correlation.[16]

Figure 4. Correlation between cartilage area and adjacent RAMRIS BME. MSI, adductor pollicis muscle signal intensity; RS, radius-scaphoid joint; SC, scaphoid-capitate joint. (Asterisks indicate (*) significant correlation).

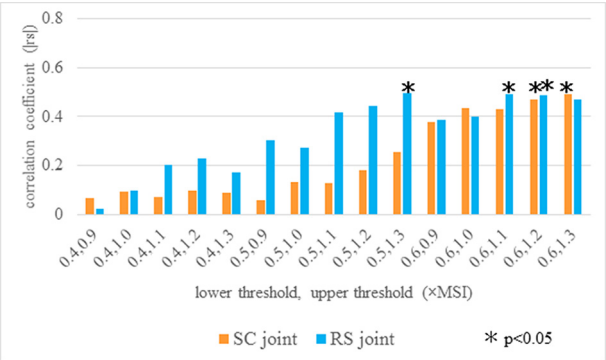
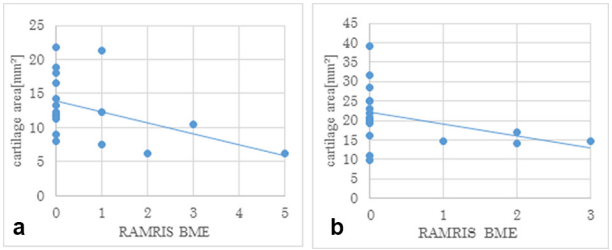


Figure 5. Correlation between cartilage area and BME. Cartilage areas were determined with thresholds of T_{lower}: MSI × 0.6 and T_{upper}: MSI × 1.2 according to the results of Figure 4a. (a) SC joint. (b) RS joint. BME, bone marrow edema; MSI, adductor pollicis muscle signal intensity; OMERACT, Outcome Measures in Rheumatology; RAMRIS, RA MRI scoring system; RS, radius-scaphoid joint; SC, scaphoid-capitate joint; T_{lower}, lower threshold; T_{upper}, upper threshold.



RESULTS

Visual assessments of joint space width, synovitis and BME

The SvdH scores using radiographs were performed for JSN in SC and RS joints of 13 patients, but JSN progression was observed in only 4 joints (three SC and one RS joints). The radiologist scored synovitis and BME at SC and RS joints of 18 patients using the RAMRIS system. Descriptive statistics (mean, standard deviation (SD), median and range) of the SvdH and RAMRIS scores in the patients are shown in Table 2.

Computer-based assessment of cartilage area

Out of 18 SC joints, one SC joint was excluded when we set the lower threshold to 0.4 and 0.5 × MSI. Out of 18 RS joints, one RS joint was excluded when the lower threshold was 0.4 × MSI. The reason was due to the included signal intensity without cartilage visually within the ROI, such as BME and artifacts derived mainly from insufficient fat suppression. Cartilage area measured by our software is shown in Table 3. Intraobserver reproducibility was 0.950 and 0.979 for SC and RS joints, respectively.

Correlation between cartilage area and RAMRIS synovitis/BME

Comparisons of cartilage area measured with each pair of thresholds by our software and adjacent RAMRIS synovitis and BME are shown in the Figure 3 and Figure 4, respectively. Cartilage area showed no significant difference with synovitis score for all sets of thresholds. On the other hand, cartilage area was associated with BME score in the thresholds (T_{lower}: MSI × 0.6,T_{upper}: MSI × 1.2) for both SC (r_s = −0.469, p < 0.05) and RS (r_s = −0.486, p < 0.05) joints (Figure 5a,b).

DISCUSSION

In this study, we developed in-house software which can quantitatively extract cartilage area on contrast enhanced T_1 weighted images. We applied the ternarization method to images of the wrist joints for cartilage segmentation and the cartilage area was correlated with BME score when thresholds were properly set for both SC and RS joints in RA patients. To the best of our knowledge, this is the first study to demonstrate that BME is

associated with quantitative cartilage loss in RA populations, although a previous study showed that synovitis and BME are associated with cartilage damage using semi-quantitative evaluation in metacarpophalangeal (MCP) joints of established RA patients.[8]

Recent studies have focused on evaluation of cartilage properties in wrist joints of healthy controls and osteomalacia patients on MR images acquired with delayed gadolinium enhanced MRI of cartilage (dGEMRIC).[17,18] The advantage of our in-house software is that it can detect cartilage area in carpal joints using conventional MR images; it takes less time to acquire images and data analysis is simpler compared to dedicated pulse sequences adopted in previous studies.[8,17–20] Furthermore, our method does not require highly trained specialists who can evaluate cartilage visually because the software only requires simple ROI placements for the measurement of the adductor pollicis MSI and for the measurement of cartilage quantification. Repeatability of our method was confirmed by almost perfect intraobserver reproducibility (ICC = 0.950 and 0.979 for SC and RS joints, respectively), which is comparable to that for dGEMRIC study of the wrist joints in healthy subjects utilizing gadoteric acid or Gd-DTPA at 3T magnet (ICC = 0.89).[18]

The visual evaluation of joint space width using the SvdH method on radiographs revealed little joint space narrowing progression. This is compatible with the observation that there is no cartilage thinning on conventional MRI in the wrist joints of early RA patients by McQueen, et al.[10] Miese, et al found significantly reduced dGEMRIC values without cartilage thickness alteration for the MCP joints of the index and middle fingers in patients with early RA, attributing glycosaminoglycan depletion of the MCP joint.[19] Our data indicate that cartilage damage may take place concurrently with bone marrow edema, which was prevalent in measured joints. The usefulness of evaluation of cartilage using contrast MRI in this study is therefore emphasized. These findings may support its predictive value in terms of cartilage destruction when BME is detected in early stages of RA patients on MR images.

This study had several limitations. First, only a small number of joints with RAMRIS BME (6 SC and 4 RS joints) were studied; the results should be confirmed in a larger patient cohort. Second, measured cartilage area may include signals from BME, soft tissue, and artifacts derived mainly from insufficient fat suppression for a simple cartilage segmentation using the ternarization method, although we hypothesized cartilage could be quantified by applying dual thresholds in contrast MRI. Finally, inter-observer reproducibility was not assessed in this study. This was because our method of cartilage segmentation is easy and simple with almost perfect intra-observer reproducibility. Further study is needed with a larger group of subjects in order to increase reliability.

In conclusion, our software can quantify cartilage using conventional MR images of the wrist. BME is associated with cartilage loss in RA patients.

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