T2 Mapping as a New Method for Quantitative Assessment of Cartilage Damage in RA

Nina Renner[1]; Arnd Kleyer[2]; Gerhard Krönke[2]; David Simon[2]; Stefan Söllner[1]; Jürgen Rech[2]; Michael Uder[3]; Rolf Janka[3]; Georg Schett[2]; Goetz H. Welsch[4]https://orcid.org/0000-0002-0757-9233
and
Milena L. Pachowsky[1]https://orcid.org/0000-0002-3729-9566

Key Indexing Terms: MRI, T2 mapping, Cartilage, anti-citrullinated peptide antibodies - positive Rheumatoid Arthritis

[1]Department of Trauma and Orthopaedic Surgery, Friedrich-Alexander-University Erlangen-Nürnberg (FAU) and Universitätsklinikum Erlangen, Erlangen, Germany

[2]Department of Internal Medicine 3, Friedrich-Alexander-University Erlangen-Nürnberg (FAU) and Universitätsklinikum Erlangen, Erlangen, Germany

[3]Department of Radiology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU) and Universitätsklinikum Erlangen, Erlangen, Germany

[4]UKE Athleticum, University Hospital of Hamburg-Eppendorf, Hamburg, Germany

Funding declaration: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.
Conflict of interest: The authors declare that they have no competing interests.

1 N R, MD; M L P, MD.

2 A K, MD; G K, MD; D S, MD; J R, MD; G S, MD

3 M U, MD; R J, MD; P S, MD

4 G H W, MD

Correspondence to:
Milena L. Pachowsky, MD
Department of Trauma and Orthopaedic Surgery
Universitätsklinikum Erlangen
Krankenhausstr. 12
91052 Erlangen
milena.pachowsky@uk-erlangen.de

Short running head: T2 mapping in RA

Abstract

Background. Rheumatoid arthritis (RA) is associated with damage of the articular cartilage and the periarticular bone. While imaging of bone damage has substantially improved in the last years, direct imaging of the articular cartilage of the hand joints in patients with RA is still challenging.

Methods. 3 Tesla Magnetic Resonance Imaging (MRI) was done in 30 RA patients and T2 relaxation times visualizing alteration in the collagen network and hydration of articular cartilage were mapped in six cartilage regions of the metacarpophalangeal joints 2 and 3. Values were related to autoantibody (anti-citrullinated peptide antibodies (ACPA), rheumatoid factor (RF)) status, disease duration, disease activity as well as sex and age of the RA patients.

Results. T2 relaxation times could be reliably measured in the six regions of the metacarpophalangeal joints. Significantly higher relaxation times indicating more advanced cartilage alterations were observed in ACPA-positive (p=0.001-0.010) and RF-positive patients (p=0.013-0.025) as well as those with longer disease duration (>3 years; p=0.028-0.043). Current disease activity, sex and age did not influence T2 relaxation times.

Conclusion. These data show that cartilage damage can be localized and quantified in the hand joints of RA patients by T2 mapping. Furthermore, ACPA and RF positivity as well as disease duration appear to be the crucial factors influencing cartilage damage.

Introduction

Rheumatoid arthritis (RA) is an inflammatory joint disease characterized by bone and cartilage damage[1,2]. While bone damage has been extensively characterized by conventional radiography, computed tomography, Magnetic Resonance Imaging (MRI) and ultrasound[3-17], the assessment of cartilage damage in RA is in its infancy. To date, only joint space narrowing on conventional radiographs provides indirect evidence for cartilage damage. This situation is in part owed to the fact that articular cartilage in the hand joints is a rather small layer and therefore challenging to assess. Recent improvements in imaging technologies, such as increased resolution and introduction of new analysis modalities may however allow closing this gap and permit to directly analyze articular cartilage of the hand joints. For instance, modern ultrasound devices with probes up to 22 megahertz allow the depiction of cartilage of metacarpophalageal (MCP) joints[18,19]. However, ultrasound is particularly user dependent and has limitations in analyzing cartilage composition[20]. New MRI techniques like delayed gadolinium enhanced MRI of cartilage (dGEMRIC) have also extended our insights into subtle structural changes of cartilage by displaying proteoglycan content after contrast enhancement. Cartilage imaging by dGEMRIC has been demonstrated in knee joints[21] as well as MCP joints of patients with RA. In the latter study, the presence of anti-citrullinated peptide antibodies (ACPA) was associated with the accelerated loss of glycosaminoglycan-content within cartilage[22-24]. An additional possibility to assess articular cartilage is T2 mapping by MRI. T2 mapping allows analyzing cartilage hydration and collagen integrity without contrast enhancement. T2 mapping has therefore been demonstrated as sensitive tool to determine cartilage damage[25-27]. However, T2 mapping, especially of the finger joints, has not yet been used to assess cartilage damages in RA. Therefore, in this study we aimed to (I) introduce T2 mapping based on 3 Tesla (T) MRI images in patients with RA, (II) to quantify

cartilage damages in the MCP joints and (III) to relate these damages to demographic and clinical data.

Materials and Methods

Patients Characteristics

Thirty RA patients fulfilling the 2010 ACR/EULAR[28] criteria of RA were analysed. The study protocol was approved by the local ethics committee (medical faculty of FAU Friedrich-Alexander University Erlangen-Nuremberg, ethics approval number 263_12 B) and written informed consent was obtained from all patients. Demographic parameters such as age and sex as well as disease-specific parameters such as disease duration, disease activity according to Disease Activity Score 28 – Erythrocyte Sedimentation Rate (DAS28-ESR)[29], presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) were recorded.

Image acquisition

All patients underwent MRI imaging of metacarpophalangeal (MCP) joints 2 and 3 of the clinically most affected hand. Imaging was performed with a 3 T whole body scanner (VERIO; SIEMENS Healthcare) by using two 4 cm-diameter surface coils (one volar, one dorsal) to perform high-resolution imaging of both MCP joints, and to enable parallel imaging techniques. Patients had to lie down in a prone position with the hand being fixed with the thumb up in a brace in order to avoid movement artefacts. The MR protocol started with morphological sequences to ensure correct positioning of the coronal sequences. Then, a multi-echo, spin-echo (SE) sequence using six echoes for T2 mapping was used (Fig. 1A). The repetition time was 1200 ms, the echo times were 15.8 ms, 31.4 ms, 47.4 ms, 63.2 ms, 79.0 ms and 94.8 ms and the flip angle was 180°. The captured area consisted of 10 slides

with a slice thickness of 1.5 mm and a field of view of 100x100mm. The corresponding pixel matrix was 384x384, the voxel size was 0.26x0.26x1.5mm, the interpolated voxel size was 0.13x0.13x1.5 mm, and the bandwidth 200 Hz/Px.

Image analysis

T2 maps were obtained using a pixel-wise, mono-exponential, non-negative least-squares-fit analysis. To avoid possible partial-volume effects, both layers were evaluated together. Region-of-interest analysis (ROI) was performed in both cartilage surfaces of the MCP joints. The ROIs were applied manually and the T2 values for each ROI were calculated automatically by the computer. The distal cartilage layer of the metacarpal bone and the proximal cartilage layer of the proximal phalanx were analysed by one imaging expert extensively trained in musculoskeletal MRI (>10 years of experience) in consensus with one orthopaedic surgeon (5 years of experience) (G.W., N.R.) (Fig. 1A and Fig. 1B). Two consecutive central slides covering MCP 2 and 3 were analysed. To detect possible regional differences within joints, three region of interests (ROIs), medial, central and lateral were assessed on coronary correlated slices (Fig. 1A).

For reliability measurements, 10 randomly selected patients were assessed on the basis of supplementary example measurements undertaken by the same observer and by a second independent one. Every assessor selected the slices anew at each assessment. The additional T2 data were collected by two independent (A.K. N.R.) investigators for all ROIs. This was used to quantify the inter-reader and the intra-reader reliability in terms of the intraclass correlation coefficient (ICC). During a patent application, one of the authors established the method for the used coil. At that time, there were both duplicate acquisitions and duplicate analyses. Since the method had already been established and was proved to be reliable before, we did not perform duplicate acquisitions.

All analyses were performed on a Leonardo Workstation (Siemens-Healthcare, Erlangen, Germany).

RAMRIS scores were evaluated for MCP joints 2 and 3.

Statistical analysis

Collection, organization and analysis were done by SPSS software for statistics (IBM SPSS 21.0, IBM corporation®, Armonk, NY, USA). Categorical variables are presented as numbers and percentages, continuous variables are provided as mean±standard deviation (SD). Assumptions of normally distributed continuous variables were tested using quantile-quantile plots as well as Kolmogorov- Smirnov and Shapiro-Wilk test. After testing for Gaussian distribution, Mann-Whitney U tests or t-tests for independent samples were applied as appropriate. T2 mapping values were compared between RA patients being younger than 50 years and older, also a comparison between patients suffering from less than 3 years and more was calculated as well as a comparison between patients being in remission or not (remission being defined as DAS28-ESR <2.6). Furthermore T2 values of patients being autoantibody positive were compared to values of autoantibody negative RA patients. Analyses for inter-reader reliability were performed using an Intra-class Correlation Coefficient (ICC). Analyses for testing the differences in the RAMRIS scores between MCP2 and MCP3 were performed using a Wilcoxon-Test. P values ≤ 0.05 were considered as statistically significant.

Results

Patient characteristics

Thirty RA patients (21 women, 9 men) with a mean age of 53.5±12.8 years were included. The disease duration was 5.8±5.8 years and disease activity was 3.3±1.6 units measured by

DAS28-ESR. Fourteen patients were ACPA and 15 RF positive. Age, sex and disease duration were comparable between the ACPA positive and ACPA negative group.

Resolution evaluation

Mean numbers of pixels for the evaluated ROIs were 80.4±20.0 (medial metacarpal head), 91.6±17.3 (central metacarpal head), 77.8±30.3 (lateral metacarpal head), 83.0±25.0 (medial phalangeal base), 92.0±22.3 (central phalangeal base) and 77.6±31.7 (lateral phalangeal base). We obtained these high values due to the ultra-high resolution of our technique.

T2 mapping in the metacarpophalangeal joints

We separately analysed the T2 values in the medial, central and lateral compartments of the second and third MCP joints. Results did not display any statistical significant difference between MCP 2 and MCP 3 joint indicating consistent results in the various joint regions within individual patients. We therefore pooled results by calculating the average T2 values of the metacarpal cartilage and the phalangeal cartilage for MCP 2 and MCP 3 joints in all further analyses.

Reliability measurements revealed an ICC of 0.915 for the inter-reader reliability and 0.905 for the intra-reader reliability.

Autoantibody status influences T2 relaxation times

Regarding ACPA status the average T2 relaxation time was higher in ACPA-positive RA patients in the vicinity of medial (41.3±15.3 vs. 29.6±7.4; p=0.010), central (43.8±14.6 vs. 28.4±10.9, p=0.001) and lateral metacarpal heads (45.6±13.8 vs. 32.0±8.6, p=0.008). Also T2 relaxation times were higher in the central (29.9±13.0 vs. 22.5±10.1, p=0.014) and lateral (37.0±15.9 vs. 28.8±12.6, p=0.039) ROI of the phalangeal bases (Table 1). T2 relaxation

times of metacarpal heads in RF positive patients showed a similar pattern of cartilage damage, showing higher T2 values compared to RF negative RA patients (Table 1).

Disease duration of rheumatoid arthritis affects T2 mapping parameters

Patients suffering from more than three years of RA showed significantly higher T2 relaxation times compared to those patients with shorter disease duration. Significant differences were observed in the medial (40.1±13.0 vs. 30.1±8.2; p=0.028), central (40.1±13.3 vs. 30.6±9.4; p= 0.043) and lateral ROI of metacarpal heads (43.6±19.1 vs. 32.4±8.9; p=0.036). In the vicinity of phalangeal bases, significant higher relaxation times were found in the medial (32.2±20.4 vs. 23.7±8.1; p=0.009) and lateral (35.8±16.9 vs. 29.3±11; p=0.04) compartment (Table 2).

Disease activity of rheumatoid arthritis and T2 mapping

We compared T2 relaxation times in patients in remission (DAS28 <2.6) versus those without remission. In all ROIs no statistically significant difference was found between remission and non-remission patients (Table 2). Concerning the correlation of T2 relaxation times with RA disease activity, we also found no significant correlation in any of the six regions investigated (correlation coefficients between -0.227 and -0.031).

T2 relaxation time regarding gender and age

T2 relaxation times in younger patients (<50 years) did not differ compared to older patients (>50 years), also no differences were found for the comparison of female and male patients (Table 2).

The comparison of the RAMRIS criteria between MCP 2 and 3 for synovitis, erosions and edema did not show statistically significant differences (synovitis MCP2 0.964 vs. MCP3 0.928, p=0.8497; erosions 1.750 vs. 1.671, p=0.515 and edema 0.428 vs. 0.356, p=0.665). The

total MCP score of 3.143 vs. 2.993 did not show a statistical significant difference either (p=0.512).

Discussion

Our study demonstrates the feasibility of T2 mapping of the articular cartilage of second and third MCP joints in RA patients. We performed a comprehensive analysis of cartilage changes at 6 different regions of the metacarpophalangeal joints. T2 relaxation times were higher in seropositive than seronegative RA patients indicating a more severe cartilage damage in autoantibody positive patients. The second factor influencing cartilage damage was disease duration, while no effects were found for the current disease activity nor age and sex of the patients.

RA is characterized by synovial inflammation that results in progressive destruction of articular cartilage as well as adjacent bone. ACPA and RF are known to be associated with increased bone damage and a more aggressive course of the disease[30,31]. Although the mechanisms leading to cartilage degradation are still not completely understood, the production of matrix cleaving enzymes by synovial inflammatory tissue is a central mechanism of cartilage degradation. Decrease in proteoglycans, changes of the collagen network and subsequent increase of cartilage permeability and water content are the earliest demonstrable changes of cartilage damage. These changes can be localized and quantified by new MR techniques like T2 relaxation time mapping[32]. In the bare area, where the bone comes into direct contact with the synovium, the contact area is larger in the proximal part of the joint[33]. The metacarpal head has more extensive contact on the surface with the synovium than the phalangeal base due to its outer shape. This could be a reason for the slightly higher

average T2 values in the metacarpal head than in the phalangeal base. In early arthritis the metacarpal head is more often affected than the phalangeal base[34].

Our data support this concept suggesting that longer exposure of the cartilage to RA-related synovitis leads to more pronounced changes. Even more interesting, the data also indicate that autoimmunity, as evidenced by ACPA and RF, augment cartilage degradation in RA. This finding is of particular clinical importance as autoimmunity develops years before the onset of arthritis[35-37]. It also extends recent imaging data that show bone and subclinical inflammatory changes in ACPA positive individuals without the presence of RA[12,13,38,39]. It is currently unclear whether ACPA or RF can directly induce metabolic changes in chondrocytes or whether autoimmune-based cartilage damage develops as the consequence of underlying bone loss or subclinical inflammation, which are found in pre-disease individuals. Markovics et al. postulate that human cartilage proteoglycans (PG) might be subjected to citrullination under inflammatory conditions[40]. Citrullinated PG could provide a local source for local citrulline autoantigens in the rheumatoid joint and might partly explain direct effects of ACPA on cartilage.

Cartilage hyper-hydration measured by T2 mapping may be a reversible process. Hence, T2 mapping could serve as a specific instrument to early detect and monitor cartilage alterations in RA patients. Thus the investigation of the cartilage layer of these pre-RA patients would be of great interest and could influence existing therapeutic algorithms. Furthermore it will be interesting to correlate changes in T2 values with the serum levels of serum cartilage biomarkers, different inflammatory cytokines or different therapeutic approaches in future studies.

Due to the very thin cartilage layer of the MCP joints it was very challenging to draw the ROIs and the surface of the 2nd and 3rd MCP is slightly bigger than the MCP IV and V joints. We indented to achieve a first overview and had to develop a protocol with realistic scan time and good image quality. The 2nd and 3rd MCP could be placed in the very center of

the coil which leads to a reduced risk of artefacts. Additionally, patients with highly active disease had difficulty keeping their hand still during the scan at all and due to the pretty long scan time, we decided to reduce the number of slices in order to have shorter scan times. At higher field strengths such as 7T it could be possible to reduce the scan time. This will be a topic for future studies in which all MCP joints will be investigated.

In our cohort of patients, we could not see a marked difference between the 2nd and 3rd MCP joints when looking at the RAMRIS scores. Hence we did not examine the MCP2 and MCP3 separately. In the present manuscript we specifically aimed to develop a rather objective and quantitative method for cartilage and joint assessment which we see as supplementary investigation with a specific focus on cartilage in order to avoid semi-quantitative assessments like RAMRIS that assesses cartilage indirectly by the presence of synovitis, erosions and joint-space narrowing. The lack of a marked difference between MCP 2 and 3 regarding the RAMRIS scores in our cohort could be caused by the relatively small number of patients. In future studies with lager patient cohorts the separate analysis of the metacarpal joints will enable an even more differentiated view of the changes in cartilage and other joint structures.

Since it is technically not easily possible to scan the MCP joints 2-4 in one acquisition session, we decided to assess the systemic effect of RA in two of the mostly affected joints in RA. We chose the 2nd and 3rd MCP joints because they could be placed in the very center of the coil which leads to a reduced risk of artefacts. Due to the very thin cartilage layer of the MCP joints it was very challenging to draw the ROIs on the surface. The 2nd and 3rd MCP joints are slightly larger than the 4th and 5th MCP joints.

Our approach with pooled values for the 2nd and 3rd MCP joints is based on our opinion that the cartilage damages are evoked by the systemic effects of RA. Moreover, it is important to state that the aim of this study is to visualize the early onset of cartilage damage in RA patients with positivity for anti-CCP antibodies prior to the occurrence of irreversible damages like joint-space narrowing, erosion, synovitis, etc.

Our study has some limitations. It is a small cross-sectional study and thus allows no drawing conclusions about the progression or reversibility of cartilage lesions. Such studies, however, will be necessary to judge about the sensitivity to change of cartilage damage in RA. Nonetheless, these data support the concept that assessment of T2 relaxation times reflects disease-specific changes of the cartilage in RA, which are influenced by disease duration and presence of autoimmunity. The lack of adjustment between systemic disease characteristics and T2 mapping values can be seen as a limitation and will be a topic for future investigations.

This study demonstrated that T2 mapping is a feasible procedure to directly detect cartilage alterations in RA patients. T2 mapping thereby allows to measure accurately hydration changes and collagen fiber damage in the cartilage. The data also show that disease duration and presence of autoantibodies appear to be the main drivers for cartilage damage in RA.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-2219.
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388:2023-2038.
3. Ostergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis 2005;64 Suppl 1:i3-7.
4. Ostergaard M, Pedersen SJ, Dohn UM. Imaging in rheumatoid arthritis--status and recent advances for magnetic resonance imaging, ultrasonography, computed tomography and conventional radiography. Best Pract Res Clin Rheumatol 2008;22:1019-1044.
5. Ostergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol 2003;30:1385-1386.
6. McQueen F, Clarke A, McHaffie A, Reeves Q, Williams M, Robinson E, et al. Assessment of cartilage loss at the wrist in rheumatoid arthritis using a new MRI scoring system. Ann Rheum Dis 2010;69:1971-1975.
7. Mandl P, Naredo E, Wakefield RJ, Conaghan PG, D'Agostino MA. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. J Rheumatol 2011;38:2055-2062.
8. Krabben A, Stomp W, van der Heijde DM, van Nies JA, Bloem JL, Huizinga TW, et al. MRI of hand and foot joints of patients with anticitrullinated peptide antibody positive arthralgia without clinical arthritis. Ann Rheum Dis 2013;72:1540-1544.
9. Krabben A, Stomp W, van Nies JA, Huizinga TW, van der Heijde D, Bloem JL, et al. MRI-detected subclinical joint inflammation is associated with radiographic progression. Ann Rheum Dis 2014;73:2034-2037.
10. Rizzo C, Ceccarelli F, Gattamelata A, Vavala C, Valesini G, Iagnocco A. Ultrasound in rheumatoid arthritis. Med Ultrason 2013;15:199-208.
11. Wakefield RJ, D'Agostino MA, Iagnocco A, Filippucci E, Backhaus M, Scheel AK, et al. The OMERACT Ultrasound Group: status of current activities and research directions. J Rheumatol 2007;34:848-851.
12. Kleyer A, Krieter M, Oliveira I, Faustini F, Simon D, Kaemmerer N, et al. High prevalence of tenosynovial inflammation before onset of rheumatoid arthritis and its link to progression to RA-A combined MRI/CT study. Semin Arthritis Rheum 2016;46:143-150.
13. Kleyer A, Finzel S, Rech J, Manger B, Krieter M, Faustini F, et al. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. Ann Rheum Dis 2014;73:854-860.
14. Stach CM, Bauerle M, Englbrecht M, Kronke G, Engelke K, Manger B, et al. Periarticular bone structure in rheumatoid arthritis patients and healthy individuals assessed by high-resolution computed tomography. Arthritis Rheum 2010;62:330-339.
15. Alcalde M, D'Agostino MA, Bruyn GA, Moller I, Iagnocco A, Wakefield RJ, et al. A systematic literature review of US definitions, scoring systems and validity according to the OMERACT filter for tendon lesion in RA and other inflammatory joint diseases. Rheumatology (Oxford) 2012;51:1246-1260.

16. Barnabe C, Feehan L. High-resolution peripheral quantitative computed tomography imaging protocol for metacarpophalangeal joints in inflammatory arthritis: the SPECTRA collaboration. J Rheumatol 2012;39:1494-1495.
17. Nieuwenhuis WP, Krabben A, Stomp W, Huizinga TW, van der Heijde D, Bloem JL, et al. Evaluation of magnetic resonance imaging-detected tenosynovitis in the hand and wrist in early arthritis. Arthritis Rheumatol 2015;67:869-876.
18. Fodor D, Felea I, Popescu D, Motei A, Ene P, Serban O, et al. Ultrasonography of the metacarpophalangeal joints in healthy subjects using an 18 MHz transducer. Med Ultrason 2015;17:185-191.
19. Hammer HB, Iagnocco A, Mathiessen A, Filippucci E, Gandjbakhch F, Kortekaas MC, et al. Global ultrasound assessment of structural lesions in osteoarthritis: a reliability study by the OMERACT ultrasonography group on scoring cartilage and osteophytes in finger joints. Ann Rheum Dis 2016;75:402-407.
20. Iagnocco A, Conaghan PG, Aegerter P, Moller I, Bruyn GA, Chary-Valckenaere I, et al. The reliability of musculoskeletal ultrasound in the detection of cartilage abnormalities at the metacarpo-phalangeal joints. Osteoarthritis Cartilage 2012;20:1142-1146.
21. Trattnig S, Marlovits S, Gebetsroither S, Szomolanyi P, Welsch GH, Salomonowitz E, et al. Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) for in vivo evaluation of reparative cartilage after matrix-associated autologous chondrocyte transplantation at 3.0T: Preliminary results. J Magn Reson Imaging 2007;26:974-982.
22. Williams A, Shetty SK, Burstein D, Day CS, McKenzie C. Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) of the first carpometacarpal (1CMC) joint: a feasibility study. Osteoarthritis Cartilage 2008;16:530-532.
23. Renner N, Kronke G, Rech J, Uder M, Janka R, Lauer L, et al. Anti-citrullinated protein antibody positivity correlates with cartilage damage and proteoglycan levels in patients with rheumatoid arthritis in the hand joints. Arthritis Rheumatol 2014;66:3283-3288.
24. Herz B, Albrecht A, Englbrecht M, Welsch GH, Uder M, Renner N, et al. Osteitis and synovitis, but not bone erosion, is associated with proteoglycan loss and microstructure damage in the cartilage of patients with rheumatoid arthritis. Ann Rheum Dis 2014;73:1101-1106.
25. Menezes NM, Gray ML, Hartke JR, Burstein D. T2 and T1rho MRI in articular cartilage systems. Magn Reson Med 2004;51:503-509.
26. Welsch GH, Apprich S, Zbyn S, Mamisch TC, Mlynarik V, Scheffler K, et al. Biochemical (T2, T2* and magnetisation transfer ratio) MRI of knee cartilage: feasibility at ultra-high field (7T) compared with high field (3T) strength. Eur Radiol 2011;21:1136-1143.
27. Buchbender C, Scherer A, Kropil P, Korbl B, Quentin M, Reichelt D, et al. Cartilage quality in rheumatoid arthritis: comparison of T2* mapping, native T1 mapping, dGEMRIC, DeltaR1 and value of pre-contrast imaging. Skeletal Radiol 2012; 41:685-692.
28. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-2581.
29. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-48.

30. Hecht C, Schett G, Finzel S. The impact of rheumatoid factor and ACPA on bone erosion in rheumatoid arthritis. Ann Rheum Dis 2015;74:e4.
31. Hecht C, Englbrecht M, Rech J, Schmidt S, Araujo E, Engelke K, et al. Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. Ann Rheum Dis 2015;74:2151-2156.
32. Lazovic-Stojkovic J, Mosher TJ, Smith HE, Yang QX, Dardzinski BJ, Smith MB. Interphalangeal joint cartilage: high-spatial-resolution in vivo MR T2 mapping--a feasibility study. Radiology 2004;233:292-296.
33. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol 2012;8:656-664.
34. Boeters DM, Nieuwenhuis WP, van Steenbergen HW, Reijnierse M, Landewe RBM, van der Helm-van Mil AHM. Are MRI-detected erosions specific for RA? A large explorative cross-sectional study. Ann Rheum Dis 2018;77:861-868.
35. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48:2741-2749.
36. Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis 2012;71:638-641.
37. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis 2013;72:1920-1926.
38. van Steenbergen HW, van Nies JA, Huizinga TW, Bloem JL, Reijnierse M, van der Helm-van Mil AH. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis 2015;74:1225-1232.
39. van de Stadt LA, Bos WH, Meursinge Reynders M, Wieringa H, Turkstra F, van der Laken CJ, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther 2010;12:R98.
40. Markovics A, Ocsko T, Katz RS, Buzas EI, Glant TT, Mikecz K. Immune Recognition of Citrullinated Proteoglycan Aggrecan Epitopes in Mice with Proteoglycan-Induced Arthritis and in Patients with Rheumatoid Arthritis. PLoS One 2016;11:e0160284.

Figure Legends

Figure 1. 3 Tesla Magnetic Resonance Imaging with T2 Mapping
(A) Enlarged morphological image of metacarpophalangeal joint 2; (B) Articular cartilage of the metacarpophalangeal joint was divided in six regions of interest (ROI; medial, central and lateral region of the metacarpal head and the phalangeal base, respectively). (C) T2 map (hybrid image) composed of the regional T2 relaxation times of metacarpophalangeal joint cartilage.

Table 1.
T2 relaxation times in the articular cartilage of RA patients dependent on inflammatory disease activity and autoantibody status.

T2 relaxation times									
ROI	Remission	No Remission	p-value	ACPA +	ACPA -	p-value	RF +	RF -	p-value
Medial MH	38.5 ± 11.9	31.2 ± 7.8	0.124	41.3 ± 15.3	29.6 ± 7.4	**0.010**	40.2 ± 12.7	29.9 ± 9.4	**0.025**
Central MH	38.2 ± 14.1	31.9 ± 8.7	0.200	43.8 ± 14.6	28.4 ± 10.9	**0.001**	40.5 ± 13.5	30.2 ± 9.2	**0.032**
Lateral MH	41.4 ± 13.3	34.7 ± 8.7	0.210	45.6 ± 13.8	32.0 ± 8.6	**0.008**	44.5 ± 13.9	32.2 ± 8.2	**0.013**
Medial PB	28.7 ± 14.1	26.9 ± 8.4	0.594	30.3 ± 14.6	25.7 ± 14.0	0.169	30.4 ± 10.9	25.2 ± 11.7	0.116
Central PB	26.7 ± 11.9	24.9 ± 7.9	0.561	29.9 ± 13.0	22.5 ± 10.1	**0.014**	27.7 ± 10.1	23.7 ± 9.1	0.152
Lateral PB	33.2 ± 14.2	27.7 ± 13.9	0.107	37.0 ± 15.9	28.8 ± 12.6	**0.039**	36.5 ± 17.1	28.8 ± 10.6	0.071

Values indicate T2 relaxation times given in milliseconds (ms); means± SD are indicated; MH, metacarpal heads; PB, phalangeal base;
ROI, regions of interest; ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor.

Table 2. T2 relaxation times in the articular cartilage of RA patients dependent on disease duration, age and sex.

T2 relaxation times									
ROI	Disease Duration <3ys	Disease Duration >3ys	p-value	Age <50 ys	Age >50 ys	p-value	Males	Females	p-value
Medial MH	30.1 ± 8.2	40.1 ± 13.0	**0.028**	35.9 ± 14.1	34.5 ± 9.1	0.725	33.8 ± 10.3	35.6 ± 11.4	0.725
Central MH	30.6 ± 9.4	40.1 ± 13.3	**0.043**	37.9 ± 13.8	33.6 ± 9.7	0.331	35.1 ± 11.5	35.5 ± 11.3	0.936
Lateral MH	32.4 ± 8.9	43.6 ± 19.1	**0.036**	37.8 ± 12.3	38.5 ± 15.4	0.977	36.9 ± 11.3	38.7 ± 15.4	0.745
Medial PB	23.7 ± 8.1	32.2 ± 20.4	**0.009**	26.9 ± 13.3	28.5 ± 15.0	0.757	30.2 ± 10.8	26.9 ± 11.5	0.370
Central PB	22.9 ± 7.0	28.6 ± 15.6	0.065	24.8 ± 10.4	26.5 ± 12.1	0.621	25.3 ± 13.3	26.1 ± 10.6	0.813
Lateral PB	29.3 ± 11.3	35.8 ± 16.9	**0.040**	32.9 ± 13.2	32.3 ± 14.7	0.823	30.4 ± 12.9	33.5 ± 14.6	0.491

Values indicate T2 relaxation times given in milliseconds (ms); means± SD are indicated; MH, metacarpal heads; PB, phalangeal base; ROI, regions of interest; ys, years.

Figure 1

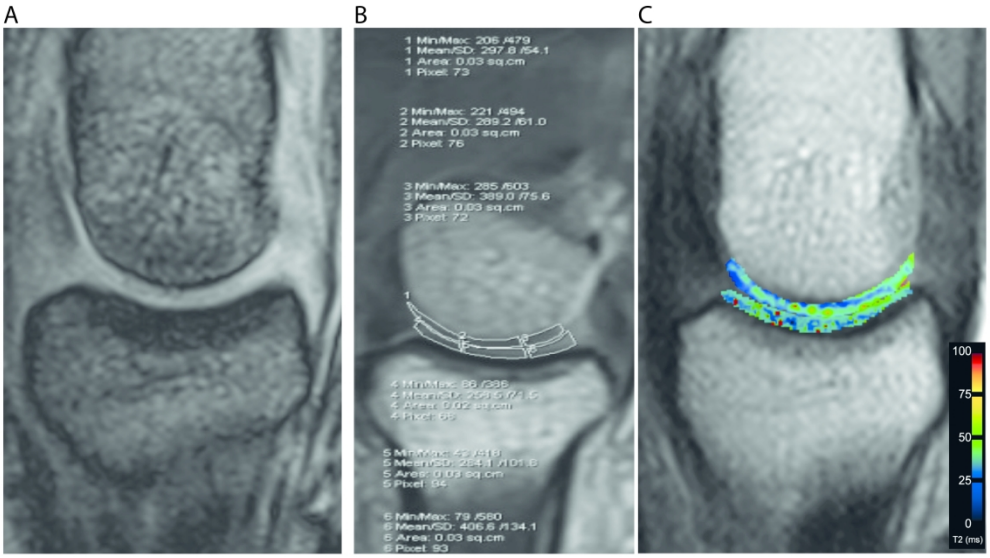

Figure 1. 3 Tesla Magnetic Resonance Imaging with T2 Mapping(A) Enlarged morphological image of metacarpophalangeal joint 2; (B) Articular cartilage of the metacarpophalangeal joint was divided in six regions of interest (ROI; medial, central and lateral region of the metacarpal head and the phalangeal base, respectively). (C) T2 map (hybrid image) composed of the regional T2 relaxation times of metacarpophalangeal joint cartilage.

671x393mm (300 x 300 DPI)