Synovial perfusion assessed by dynamic contrast-enhanced MRI is associated to treatment response, remission, and cartilage quality in rheumatoid arthritis

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Key messages: Synovial perfusion measured by DCE-MRI relates to therapy response and remission in early RA patients. High scores in DCE-MRI perfusion were significantly associated to a lower cartilage quality.

Abstract

Objective: To assess associations of synovial perfusion, cartilage quality and outcome in rheumatoid arthritis (RA).

Methods: Synovial perfusion and cartilage quality were assessed by dynamic contrast-enhanced magnetic resonance imaging in metacarpophalangeal joints of 28 treatment-naïve RA patients at baseline, 3 and 6 months after methotrexate. Analysis was by linear mixed modelling.

Results: Synovial perfusion parameters were associated to remission ($p<0.05$) and cartilage quality ($p<0.004$). Maximum synovial enhancement was associated to EULAR response ($p<0.05$). Synovial perfusion improved in non-responders over time ($p<0.05$).

Conclusion: Synovial perfusion relates to remission, response, and cartilage quality in a cohort of therapy naïve, early RA patients.

Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in rheumatoid arthritis (RA) permits assessment of synovial perfusion and reflects histological signs of synovitis in RA (1) and relate to systemic disease activity (2). Hence, DCE-MRI theoretically offers the possibility for an objective evaluation of disease activity. Current response criteria partially rely on patient reported outcomes, e.g. a patient global and reported joint pain informing the DAS28 (3). This may result in overestimation of disease activity (3), even though the subjective components are sensitive to change (4). Conversely, undertreatment of patients which show a progressive disease course despite clinical remission may also occur, a situation sometimes referred to as 'silent progression' (5). Moreover, growing evidence suggests that early and continuing cartilage damage is of paramount importance in the pathogenesis of RA (6). Cartilage damage in turn can be assessed in finger joints of RA patients by non-invasive means employing delayed Gadolinium-enhancement MRI (dGEMRIC), for instance (7).

We therefore assessed active, treatment-naïve RA patients, who were started on methotrexate therapy by MRI in order to determine how DCE-MRI relates to remission, response, and cartilage quality.

Methods

Patients and protocol

Treatment-naïve patients with RA according to 2016 ACR/EULAR criteria (n = 28, mean age 55 ± 11.4 years, 19 female,disease duration ≤ 6month, Ø 16.3 weeks; min. 2 weeks, max. 23 weeks; all patients were pos. for Rheumatoid Factor (Ø RF 215 IU/ml; Min 24, Max 2314 IU/ml and CCP Antibodies (Ø CCP antibodies 131 U/ml; Min 5, Max >200 U/ml); DAS28 baseline Ø 4.7 (SD 0.85; Min 3.3, Max 6.3); DAS28 3 month Ø 3.5 (SD1.3, Min 1.6, Max 6.2); DAS28 6 month Ø 2.6 (SD 0.83,Min 1.6, Max 4.8) from the outpatient department of Heinrich-Heine-University Düsseldorf, Germany were consecutively enrolled. DAS28 with CRP, and an MRI of the dominantly involved hand were assessed at baseline, and at 3 and 6 months after initiation of methotrexate therapy (15 mg s.c. weekly). Exclusion criteria consisted in pregnancy, age < 18 years, claustrophobia, contraindications for either MRI (e.g. metal implants) or Gadolinium (e.g. allergy). Treatment response and remission were defined according to EULAR criteria. The study was approved by the Ethics Committee of the Medical Faculty of Heinrich-Heine-University Düsseldorf, Germany (study number 3828). All patients provided written informed consent.

MRI protocol

3-Tesla MRI (Magnetom Trio A Tim System; Siemens Healthcare, Erlangen, Germany) was used to obtain DCE-MRI and dGEMRIC scans of MCP joints 2 and 3. DCE-MRI imaging was performed with a multi-slice T1-weighted turbo-flash sequence (8). The contrast agent (Gd-DTPA, Magnevist; Schering) was applied twenty seconds after the sequence start as previously described (7). Briefly, maximum contrast enhancement (ME), maximum synovial volume (MV), and rate of contrast enhancement after 17s (RE) were calculated for further analyses.

dGEMRIC imaging sequences were obtained 40 minutes after injection of 0.4 mL/kg body weight gadolinium. 3D FLASH imaging was performed, as previously described (8). MRI protocols including data processing are detailed in supplement 1. MRI investigators (CS, AML, FF, ME) were blinded to the clinical information and other imaging information such as sonography or conventional x-rays.

Statistical analysis

Linear mixed modelling with a random intercept for patient identity and adjustments for age and gender were performed with DCE-MRI parameters (ME, MV, RE) as the dependent variables, and remission or response, and the time point as independent variables. Additionally, dGEMRIC values were used as dependent with DCE-MRI parameters as independent variables along with the above adjustments. A p-value < 0.05 was considered significant. In order to verify model assumptions, we relied on inspection of (1) plotting model residuals vs. predicted value to check for linearity, (2) qq-ploting to check for normal distribution of residuals, (3) leverage plotting with ANOVA to check for homogeneity of variance. All statistical analyses were performed with the statistical software R, version 3.4.1 (The R Foundation for Statistical Computing).

Results

In order to measure synovial perfusion, DCE-MRI was conducted. Distinct parameters related to contrast enhancement (MV, ME, RE) were used for further analyses. EULAR remission criteria were met by 5 patients (17.9%) at 3 months, and 12 patients (42.9%) at 6 months. Remission was associated to significantly lower values for all DCE-MRI parameters in both joints assessed, with the highest magnitude of effect for ME (table 1a) (figures 1 and 2).

EULAR moderate or good response criteria were met by 7 (25%) and 9 (32.1%) patients at 3 months, and by 2 (7.1%) and 10 (35.7%) patients at 6 months, respectively. Any treatment response (good or moderate) was associated to lower ME, but not MV or RE in both joints (table 1a). Next, cartilage quality was assessed by dGEMRIC and compared to DCE-MRI. High scores in any DCE-MRI perfusion parameter were significantly associated to a lower cartilage quality, with the highest magnitude of effect for MV and RE (table 1a).

EULAR remission and response incorporate subjective measures such as tender joint count and patient global assessment. We were therefore interested in the time course of perfusion in patients not satisfying remission or response criteria under methotrexate therapy. All DCE-MRI parameters improved over time under methotrexate therapy even in patients not satisfying remission or treatment response criteria. This association was significant for both joints and all parameters assessed with the exception of a borderline significance for ME in MCP3 joints in association to response (table 1b).

Discussion

Histological synovial inflammation, especially sublining CD68 macrophages range amongst the best parameters to detect treatment response in RA. These markers do not seem to be influenced by placebo effects (9). However, the determination of synovial inflammation by histological means is limited by the necessity of invasive procedures. We have previously shown that DCE-MRI reflects histological signs of synovitis in RA (1) and may therefore potentially substitute invasive techniques. Our current study expands on this knowledge by demonstrating that DCE-MRI parameters consistently relate to remission and response as defined by the compound measures DAS28 according to EULAR definition.

Of the different DCE-MRI parameters assessed, ME was the only significant predictor of response, while remission was predicted by MV and RE as well. Of note, the magnitude of effect (represented by the 'Estimate' in table 1) was consistently highest for ME which suggests that ME is the best parameter for determination of treatment response and remission. Conversely, cartilage quality (dGEMRIC) was more closely associated to RE or MV as opposed to ME ('Estimate' in the 'dGEMRIC' columns of table 1a). Thus, our data suggest that the different perfusion parameters are complementary in their information on synovial perfusion and cartilage quality.

We previously reported that patients in clinical remission or responding to therapy may show a progressive disease course when additionally analyzed by MRI, a situation also referred to as silent progression (5). Interestingly, our current results suggest that the opposite may hold true as well: patients who did not reach remission according to clinical criteria showed reduced synovial perfusion over time. We speculate that this is a consequence of treatment effectivity as opposed to the natural course of the disease. A number of subgroup analyses of randomized controlled trials with the use of DCE-MRI sequences support this notion (10–12).

In contrast, MRI may also unmask erosive disease in successfully treated patients (13) and bone marrow edema is a major risk factor for future erosive disease (14). Thus, MRI may help to prevent both over- and undertreatment of RA patients. Of note, our assumptions are based on previous literature and the results presented. The generalizability of our data is however limited due to the small sample size. Hence, more data is needed before firm conclusions can be drawn in this regard. Furthermore, whether remission defined by MRI more accurately predicts favorable outcomes (e.g. functionality, erosive disease on conventional x-rays) than established and validated clinical criteria such as the DAS28 is under debate (15). The increased costs of an MRI-based outcome criterion as opposed to a clinical criterion also have to be kept in mind. Additionally, our protocol involved the application of gadolinium as a contrast agent and concerns have been raised concerning the safety of gadolinium use (16). However, contrast free sequences are being developed and may render the use of gadolinium unnecessary for some indications of MRI in the future (17).

Growing evidence suggests that cartilage injury is paramount in the perpetuation of RA and potentially even a key inciting component in RA pathogenesis (6). The current study supports this concept by demonstrating that proteoglycan loss evidenced by a reduced dGEMRIC index is associated to increased synovial perfusion in early RA patients. We did not find improved cartilage quality in either remitting patients, responding patients, or in the time-course under methotrexate therapy, however. This may reflect a lack of cartilage repair despite effective treatment over time (18). The functional long-term impact of reduced cartilage quality is well documented (18,19), emphasizing the importance to protect cartilage integrity.

In conclusion, synovial tissue perfusion relates to remission, response, and cartilage quality assessed by MRI in a cohort of therapy-naïve, early RA patients.

Declarations

Availability of supporting data: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Study design: PS, CS, RB, MS, BO and SV. Study conduct: PS, CS, BO and SV. Data collection: PS, CS, RB, MS, BO and SV. Data analysis: PS, CS, RB, AML, FF, ME, MS, BO and SV. Data interpretation: PS, CS, RB, AML, FF, ME, MS, BO and SV. Drafting manuscript: PS and SV. Revising manuscript content PS, CS, RB, AML, FF, ME, MS, BO and SV take responsibility for the integrity of the data analysis. All authors read and approved the final manuscript.

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References

1. Vordenbäumen S, Schleich C, Lögters T, Sewerin P, Bleck E, Pauly T, et al. Dynamic contrast-enhanced magnetic resonance imaging of metacarpophalangeal joints reflects histological signs of synovitis in rheumatoid arthritis. Arthritis Res Ther 2014;16:452.

2. Vordenbäumen S, Sewerin P, Lögters T, Miese F, Schleich C, Bleck E, et al. Inflammation and vascularisation markers of arthroscopically-guided finger joint synovial biospies reflect global disease activity in rheumatoid arthritis. Clin Exp Rheumatol 2014;32:117-20.

3. Son KM, Lee SY, Seo YI, Choi J-E, Kim HA. Contribution of subjective Disease Activity Score 28 (DAS28) components to the response to treatment of rheumatoid arthritis. Clin Rheumatol 2017;36:1221-7.

4. Jurgens MS, Overman CL, Jacobs JWG, Geenen R, Cuppen BVJ, Marijnissen ACA, et al. Contribution of the subjective components of the disease activity score to the response to biologic treatment in rheumatoid arthritis. Arthritis Care Res 2015;67:923-8.

5. Sewerin P, Vordenbaeumen S, Hoyer A, Brinks R, Buchbender C, Miese F, et al. Silent progression in patients with rheumatoid arthritis: is DAS28 remission an insufficient goal in RA? Results from the German Remission-plus cohort. BMC Musculoskelet Disord 2017;18:163.

6. Pap T, Korb-Pap A. Cartilage damage in osteoarthritis and rheumatoid arthritis--two unequal siblings. Nat Rev Rheumatol 2015;11:606-15.

7. Miese F, Buchbender C, Scherer A, Wittsack H-J, Specker C, Schneider M, et al. Molecular imaging of cartilage damage of finger joints in early rheumatoid arthritis with delayed gadolinium-enhanced magnetic resonance imaging. Arthritis Rheum 2012;64:394-9.

8. Schleich C, Müller-Lutz A, Sewerin P, Ostendorf B, Buchbender C, Schneider M, et al. Intra-individual assessment of inflammatory severity and cartilage composition of finger joints in rheumatoid arthritis. Skeletal Radiol 2015;44:513-8.

9. de Hair MJH, Harty LC, Gerlag DM, Pitzalis C, Veale DJ, Tak PP. Synovial tissue analysis for the discovery of diagnostic and prognostic biomarkers in patients with early arthritis. J Rheumatol 2011;38:2068-72.

10. Beals C, Baumgartner R, Peterfy C, Balanescu A, Mirea G, Harabagiu A, et al. Magnetic resonance imaging of the hand and wrist in a randomized, double-blind, multicenter, placebo-controlled trial of infliximab for rheumatoid arthritis: Comparison of dynamic contrast enhanced assessments with semi-quantitative scoring. PloS One 2017;12:e0187397.

11. Waterton JC, Ho M, Nordenmark LH, Jenkins M, DiCarlo J, Guillard G, et al. Repeatability and response to therapy of dynamic contrast-enhanced magnetic resonance imaging biomarkers in rheumatoid arthritis in a large multicentre trial setting. Eur Radiol 2017;27:3662-8.

12. Conaghan PG, Østergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Ann Rheum Dis 2016;75:1024-33.

13. Tamai M, Kawakami A, Uetani M, Takao S, Arima K, Iwamoto N, et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. Arthritis Rheum 2009;61:772-8.

14. Haavardsholm EA, Lie E, Lillegraven S. Should modern imaging be part of remission criteria in rheumatoid arthritis? Best Pract Res Clin Rheumatol 2012;26:767-85.

15. van Tuyl LHD, Felson DT, Wells G, Smolen J, Zhang B, Boers M, et al. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res 2010;62:108-17.

16. Runge VM. Critical Questions Regarding Gadolinium Deposition in the Brain and Body After Injections of the Gadolinium-Based Contrast Agents, Safety, and Clinical Recommendations in Consideration of the EMA's Pharmacovigilance and Risk Assessment Committee Recommendation for Suspension of the Marketing Authorizations for 4 Linear Agents. Invest Radiol 2017;52:317-23.

17. Rehnitz C, Kupfer J, Streich NA, Burkholder I, Schmitt B, Lauer L, et al. Comparison of biochemical cartilage imaging techniques at 3 T MRI. Osteoarthritis Cartilage 2014;22:1732-42.

18. Schett G, Coates LC, Ash ZR, Finzel S, Conaghan PG. Structural damage in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: traditional views, novel insights gained from TNF blockade, and concepts for the future. Arthritis Res Ther 2011;13 Suppl 1:S4.

19. Hayer S, Bauer G, Willburger M, Sinn K, Alasti F, Plasenzotti R, et al. Cartilage damage and bone erosion are more prominent determinants of functional impairment in longstanding experimental arthritis than synovial inflammation. Dis Model Mech 2016;9:1329-38.

Figure 1

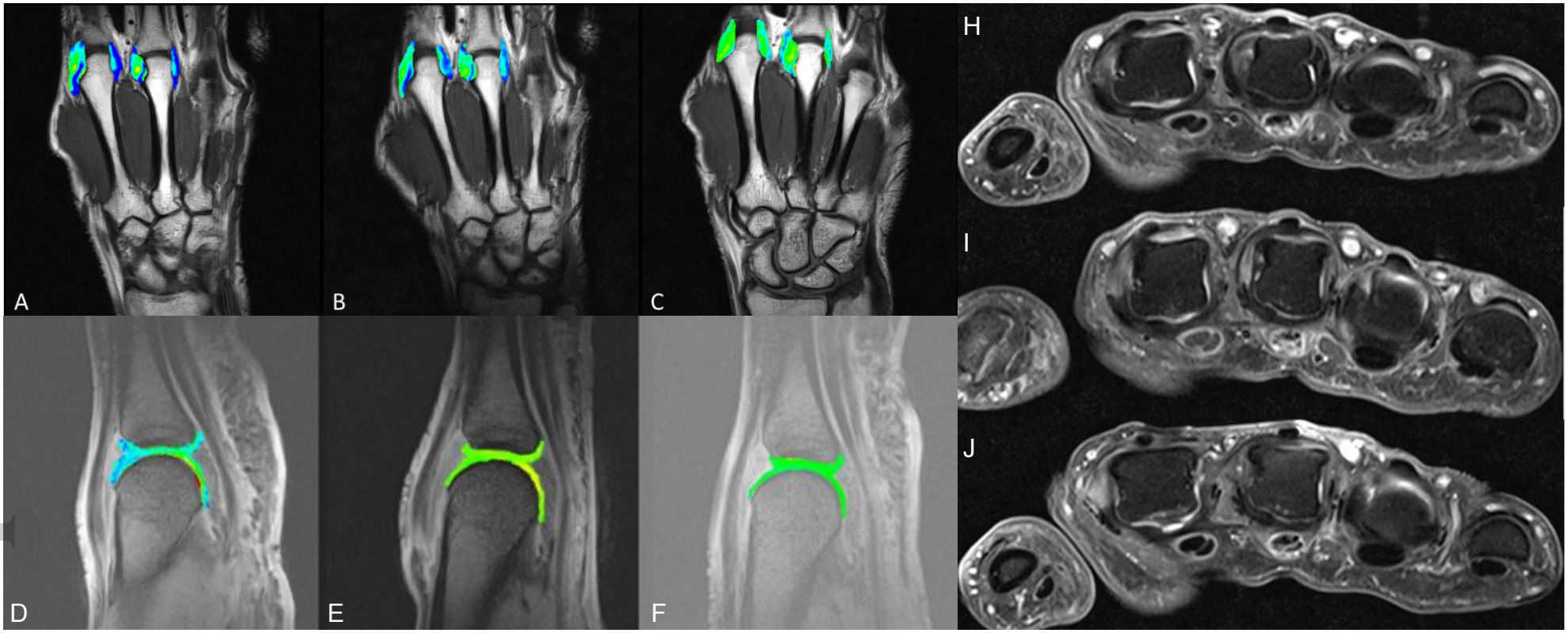

Figure 2:

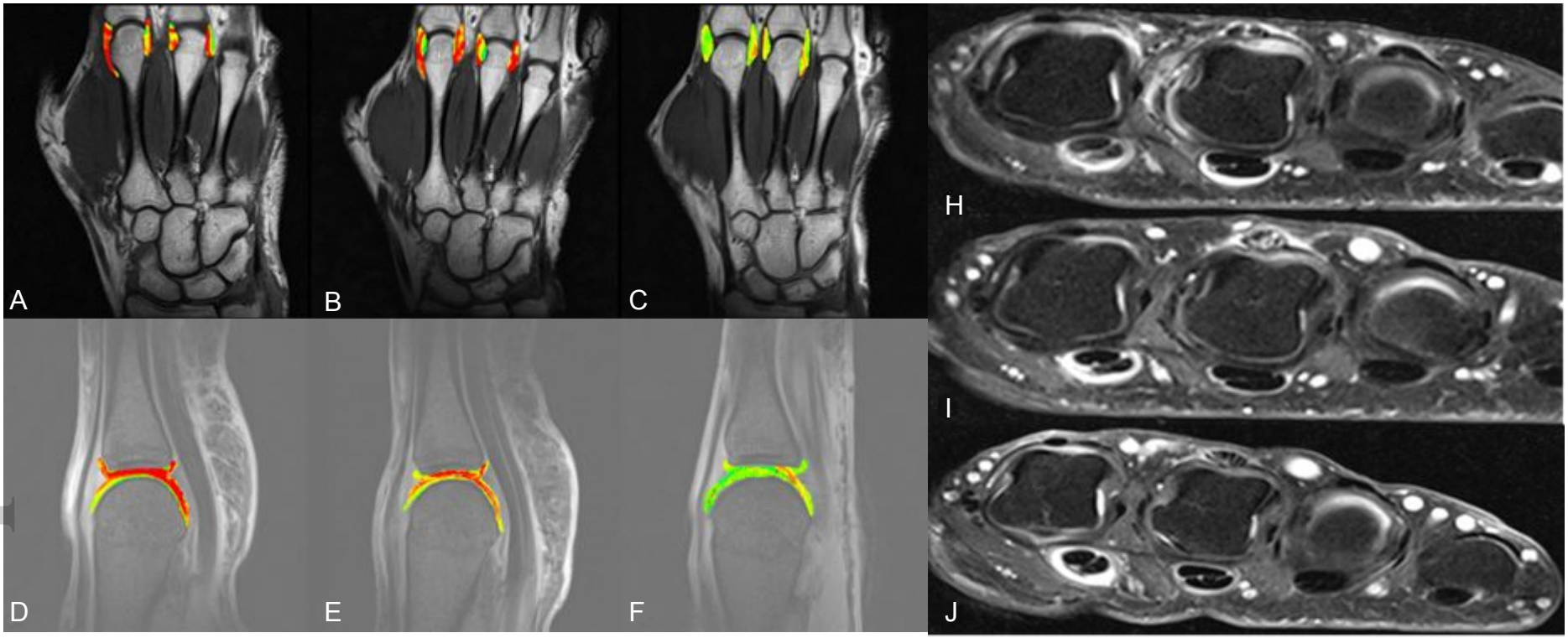

Figure Legends

Fig. 1. Picture **A - C:** Overlay of native T1 image of digitus 2 and 3 with colour-coded map of dynamic MRI from blue - low perfusion to red - high perfusion of MCP D2 and D3. Picture A demonstrated the perfusion of MCP joints at baseline MRI prior to MTX therapy, picture B and C showed the perfusion after 3 and 6 months after MTX therapy. In this example, we found higher perfusion after 3 and 6 months compared to baseline MRI for both MCP joints. Picture D - F showed a colour-coded dGEMRIC map of MCP D2 from blue - high GAG content to red - low GAG content. In correlation with dynamic MRI, dGEMRIC analysis demonstrated an increasing GAG loss after 3 and 6 months after MTX therapy (picture E and F) compared to baseline MRI (picture D) in this case. Picture H – J illustrated axial fat suppressed T1 images after application of contrast agent of MCP joints. Morphological synovitis subscore according to RAMRIS showed moderate synovitis at baseline and after 3 months MTX therapy of MCP D2 (picture H and I). 6 months after MTX therapy, we found high synovitis subscore in MCP D2 (picture J) in this patient. This is in accordance with our analysis demonstrating a significant correlation of perfusion and synovitis subscore 6 months after the beginning of MTX therapy.

Fig. 2. Picture A – C: Overlay of native T1 image of digitus 2 and 3 with colour-coded map of dynamic MRI from blue - low perfusion to red - high perfusion of MCP D2 and D3. Picture A demonstrated the perfusion of MCP joints at baseline MRI prior to MTX therapy, picture B and C showed the perfusion after 3 and 6 months after MTX therapy. In this example, we found higher perfusion at baseline MRI compared to follow up measurements after 3 and 6 monaths initiating MTX therapy. Picture D – F showed colour-coded dGEMRIC map of MCP D2 from blue - high GAG content to red - low GAG content. In correlation with dynamic

MRI, dGEMRIC analysis demonstrated lower dGEMRIC index after 3 and 6 months initiating MTX therapy (picture E and F) compared to baseline MRI (picture D) in this case. Picture H – J illustrated axial fat suppressed T1 images after application of contrast agent of MCP joints. Morphological synovitis subscore according to RAMRIS showed high synovitis of MCP D2-D4 at baseline MRI (picture H). After 3 and 6 months MTX therapy, we found lower synovitis subscore in MCP D2 - D4 (picture I and J) in this patient.

Table 1

A

Joint	DCI-MRI	Remission			Response			dGEMRIC		
		E	SE	P	E	SE	P	E	SE	P
MCP2	ME	-15.6	6.7	0.02	-48.5	22.5	0.03	-0.8	0.2	<0.0001
	MV	-0.5	0.2	0.01	-1-3	0.8	0.09	-18.1	4.9	<0.001
	RE	-0.3	0.2	0.04	-0.9	0.6	0.11	-31.5	6.3	<0.0001
MCP3	ME	-8.7	3.8	0.02	-28.4	13.5	0.03	-1.1	0.3	<0.0001
	MV	-0.4	0.2	0.02	-0.6	0.6	0.28	-24.7	8.6	0.004
	RE	-0.3	0.1	<0.01	-0.5	0.4	0.23	-38.4	11.6	<0.001

B

Joint	DCI-MRI	Non-remission with MTX over time			Non-response with MTX over time		
		E	SE	P	E	SE	P
MCP2	ME	-15.6	6.7	0.02	-15.5	7.0	0.03
	MV	-0.6	0.2	0.01	-0.7	0.2	0.005
	RE	-0.3	0.2	0.04	-0.4	0.2	0.02
MCP3	ME	-8.7	3.8	0.02	-7.7	4.0	0.06
	MV	-0.4	0.2	0.02	-0.4	0.2	0.02
	RE	-0.3	0.1	0.009	-0.3	0.1	0.01

Table 1

A. Associations of synovial perfusion imaging with outcome and cartilage quality. Dynamic contrast-enhanced MRI (DCE-MRI) was used to calculate maximum synovial enhancement (ME), maximum synovial volume (MV) and the rate of synovial enhancement (RE) in metacarpophalangeal (MCP) 2 and 3 joints of 28 rheumatoid arthritis patients. DCI-MRI parameters were associated with EULAR remission, EULAR good or moderate vs. no response, and cartilage quality (delayed Gadolinium enhancement (dGEMRIC)) by linear mixed modelling (E, estimate; SE, standard error; P, p-value).

B Time course of synovial perfusion in non-remitting or non-responding patients receiving methotrexate. Dynamic contrast-enhanced MRI (DCI-MRI) was used to calculate maximum synovial enhancement (ME), maximum synovial volume (MV) and the rate of synovial enhancement (RE) in metacarpophalangeal (MCP) 2 and 3 joints of non-remitting or non-responding rheumatoid arthritis patients according to EULAR criteria who received methotrexate therapy. Associations according to linear mixed modelling (E, estimate; SE, standard error; P, p-value).