Assessing Associations of Synovial Perfusion, Cartilage Quality, and Outcome in Rheumatoid Arthritis Using Dynamic Contrast-enhanced Magnetic Resonance Imaging

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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-naive patients with RA at baseline and at 3 and 6 months after methotrexate. Analysis was by linear mixed modeling.

Results. Synovial perfusion variables were associated with remission ($p < 0.05$) and cartilage quality ($p < 0.004$). Maximum synovial enhancement was associated to European League Against Rheumatism response ($p < 0.05$). Synovial perfusion improved in nonresponders over time ($p < 0.05$).

Conclusion. Synovial perfusion relates to remission, response, and cartilage quality in a cohort of therapy-naive patients with early RA. (J Rheumatol First Release July 15 2019; doi:10.3899/jrheum.180832)

Key Indexing Terms:
RHEUMATOID ARTHRITIS REMISSION RESPONSE PREDICTION CARTILAGE

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 relates 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., patient global and reported joint pain informing the 28-joint count Disease Activity Score (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 who 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 noninvasive means using delayed gadolinium enhancement MRI of cartilage (dGEMRIC), for instance[7].

We therefore assessed by MRI a group of active, treatment-naive patients with RA [who began methotrexate (MTX) therapy] to determine how DCE-MRI relates to remission, response, and cartilage quality.

MATERIALS AND METHODS

Patients and protocol. Treatment-naive patients with RA according to the 2016 American College of Rheumatology/European League Against Rheumatism (EULAR) criteria [n = 28, mean age 55 ± 11.4 yrs, 19 female, disease duration ≤ 6 months (mean 16.3 weeks; range 2–23 weeks); all patients were positive for rheumatoid factor (mean RF 215 IU/ml; range 24–2314 IU/ml) and cyclic citrullinated peptide antibodies (mean 131 U/ml; range 5 to > 200 U/ml); DAS28 baseline mean 4.7 (SD 0.85; range 3.3–6.3); 3-month DAS28 mean 3.5 (SD 1.3; range 1.6–6.2); 6-month DAS28 2.6 (SD

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0.83; range 1.6–4.8)] from the outpatient department of Heinrich-Heine-University, Düsseldorf, Germany, were consecutively enrolled. DAS28 with C-reactive protein, and an MRI of the dominantly involved hand were assessed at baseline, and at 3 and 6 months after initiation of MTX therapy (15 mg subcutaneous weekly). Exclusion criteria consisted of pregnancy, age < 18 years, claustrophobia, and 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) was used to obtain DCE-MRI and dGEMRIC scans of metacarpophalangeal (MCP) joints 2 and 3. DCE-MRI imaging was performed with a multislice T1-weighted turbo-flash sequence[8]. The contrast agent (Gd-DTPA, Magnevist; Schering) was applied 20 s after the sequence start as previously described[7]. Briefly, maximum contrast enhancement (ME), maximum synovial volume (MV), and rate of contrast enhancement after 17 s (RE) were calculated for further analyses. The dGEMRIC imaging sequences were obtained 40 min after injection of 0.4 ml/kg body weight gadolinium. As previously described, 3-D FLASH imaging was performed[8]. MRI protocols including data processing are detailed in the Supplementary Data (available from the authors on request). MRI investigators (CS, AML, FF, ME) were blinded to the clinical information and other imaging information such as sonography or conventional radiographs.

Statistical analysis. Linear mixed modeling with a random intercept for patient identity and adjustments for age and sex were performed with DCE-MRI variables (ME, MV, RE) as the dependent variables, and remission or response, and the timepoint as independent variables. Additionally, dGEMRIC values were used as dependent with DCE-MRI variables and as independent variables along with the above adjustments. A p value < 0.05 was considered significant. To verify model assumptions, we relied on inspection of (1) plotting model residuals versus predicted value to check for linearity; (2) QQ-plotting to check for normal distribution of residuals; and (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

To measure synovial perfusion, DCE-MRI was conducted. Distinct variables 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 with significantly lower values for all DCE-MRI variables in both joints assessed, with the highest magnitude of effect for ME (Table 1A, Figure 1, Figure 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 variable were significantly associated with 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's global assessment. We were therefore interested in the time course of perfusion in patients not satisfying remission or response criteria under MTX therapy. All DCE-MRI variables improved over time under MTX therapy even in patients not satisfying remission or treatment response criteria. This association was significant for both joints and all variables 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, ranks among the best variables 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 substitute for invasive techniques. Our current study expands on this knowledge by demonstrating that DCE-MRI variables consistently relate to remission and response as defined by the compound measures (DAS28) according to EULAR definition.

Of the different DCE-MRI variables 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 Estimates in Table 1) was consistently highest for ME, which suggests that ME is the best variable for the determination of treatment response and remission. Conversely, cartilage quality (dGEMRIC) was more closely associated with RE or MV as opposed to ME (estimates in the dGEMRIC columns of Table 1A). Thus, our data suggest that the different perfusion variables 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[10,11,12]. 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 patients with RA. Of note, our assumptions are based on previous literature and the results presented. The generalizability of our data is however limited owing to the small sample size. Hence, more data is needed before firm conclusions can be drawn in this regard. Further, whether remission defined by MRI more accurately predicts favorable outcomes (e.g., functionality,

Table 1A. Associations of synovial perfusion imaging with outcome and cartilage quality.

Joint	DCE-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

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 MCP2 and MCP3 of 28 rheumatoid arthritis patients. DCE-MRI variables were associated with EULAR remission, EULAR good or moderate vs no response, and cartilage quality (dGEMRIC) by linear mixed modeling. MRI: magnetic resonance imaging; dGEMRIC: delayed gadolinium enhancement MRI of cartilage; E: estimate; SE: standard error; MCP: metacarpophalangeal joint; EULAR: European League Against Rheumatism.

Table 1B. Time course of synovial perfusion in nonremitting or nonresponding patients receiving methotrexate (MTX).

Joint	DCE-MRI	Nonremission with MTX over Time			Nonresponse 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

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 MCP2 and MCP3 of nonremitting or nonresponding rheumatoid arthritis patients (according to EULAR criteria) who received methotrexate therapy. Associations were according to linear mixed modeling. MRI: magnetic resonance imaging; E: estimate; SE: standard error; MCP: metacarpophalangeal joint; EULAR: European League Against Rheumatism.

erosive disease on conventional radiographs) 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 about 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 with increased synovial perfusion in patients with early RA. We did not find improved cartilage quality in either remitting patients, responding patients, or in the time course under MTX therapy, however. This may reflect a lack of cartilage repair despite effective treatment over time[18]. The functional longterm effect of reduced cartilage quality is well documented[18,19], emphasizing the importance of protecting cartilage integrity.

Synovial tissue perfusion relates to remission, response, and cartilage quality assessed by MRI in a cohort of therapy-naive patients with early RA.

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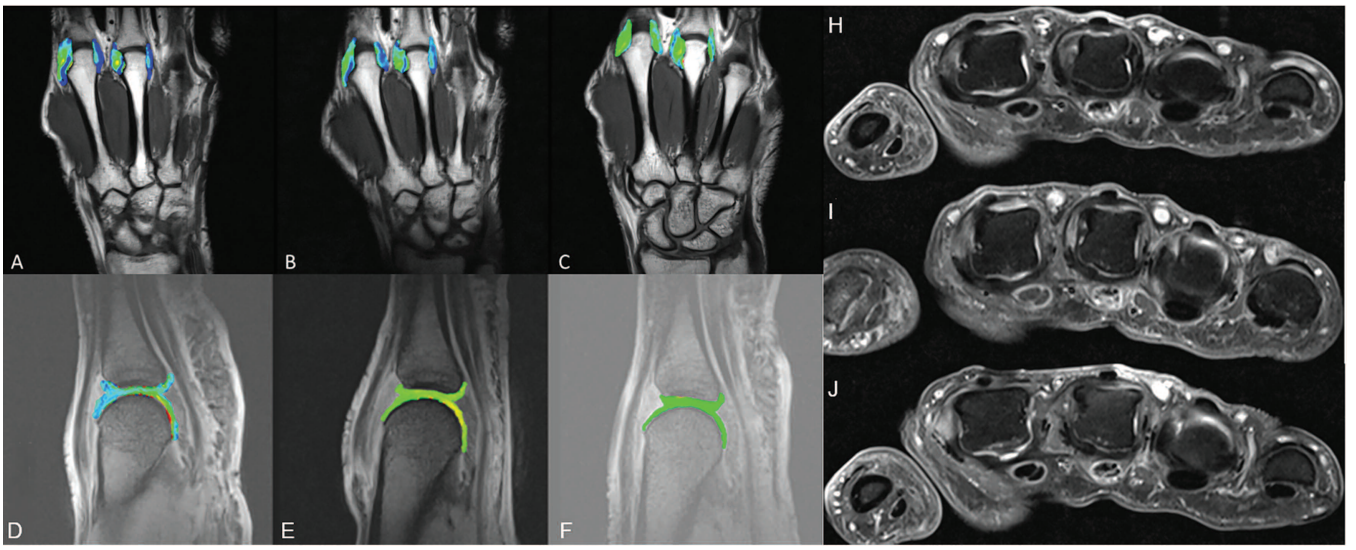

Figure 1. A–C. Overlay of native T1 image of digitus 2 and 3 with color-coded map of dynamic MRI from blue (low perfusion) to red (high perfusion) of MCP joints 2 and 3. Panel A demonstrated the perfusion of MCP joints at baseline MRI prior to MTX therapy; panels B and C showed the perfusion after 3 and 6 months after MTX therapy, respectively. In this example, we found higher perfusion after 3 and 6 months compared to baseline MRI for both MCP joints. D–F. Color-coded dGEMRIC map of MCP joint 2 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 of MTX therapy (E and F) compared to baseline MRI (D) in this case. H–J. 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 joint 2 (H and I). Six months after MTX therapy, we found high synovitis subscore in MCP joint 2 (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. MRI: magnetic resonance imaging; MCP: metacarpophalangeal; GAG: glycosaminoglycan; dGEMRIC: delayed gadolinium enhancement MRI of cartilage; MTX: methotrexate; RAMRIS: rheumatoid arthritis magnetic resonance imaging scoring.

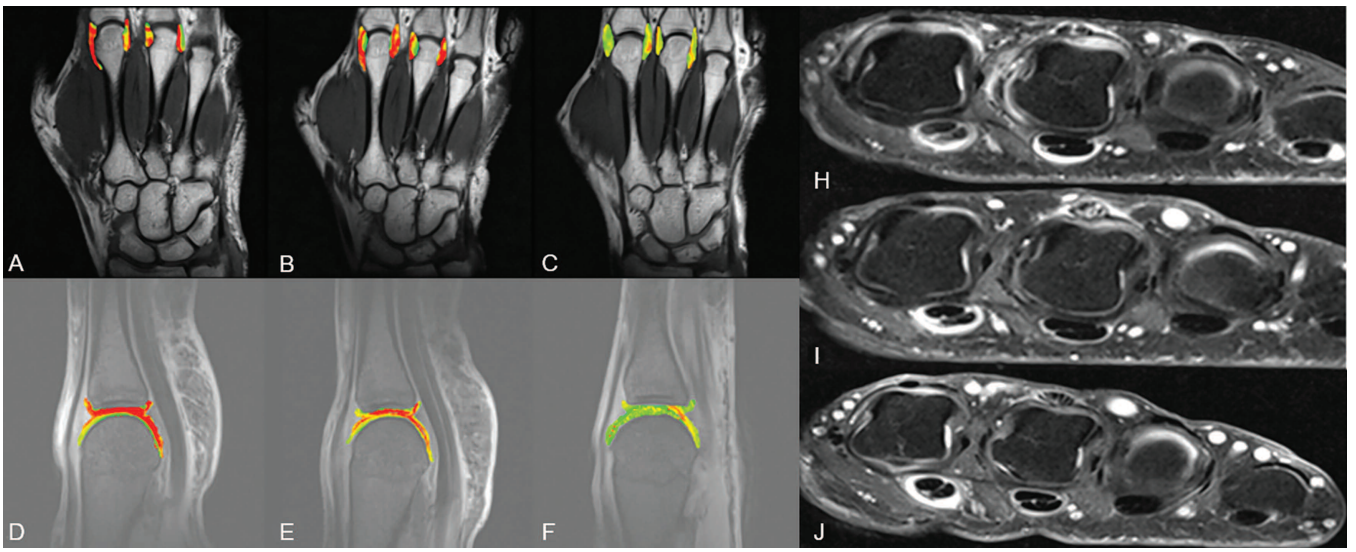

Figure 2. A–C. Overlay of native T1 image of digitus 2 and 3 with color-coded map of dynamic MRI from blue (low perfusion) to red (high perfusion) of MCP joints 2 and 3. Panel A demonstrated the perfusion of MCP joints at baseline MRI prior to MTX therapy; panels B and C showed the perfusion after 3 and 6 months after MTX therapy, respectively. In this example, we found higher perfusion at baseline MRI compared to followup measurements after 3 and 6 months initiating MTX therapy. D–F. Color-coded dGEMRIC map of MCP joint 2 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 of MTX therapy (E and F) compared to baseline MRI (D) in this case. H–J. Axial fat-suppressed T1 images after application of contrast agent of MCP joints. Morphological synovitis subscore according to RAMRIS showed high synovitis of MCP joints 2–4 at baseline MRI (H). After 3 and 6 months of MTX therapy, we found lower synovitis subscore in MCP joints 2–D4 (I and J) in this patient. MRI: magnetic resonance imaging; MCP: metacarpophalangeal; GAG: glycosaminoglycan; dGEMRIC: delayed gadolinium enhancement MRI of cartilage; MTX: methotrexate; RAMRIS: rheumatoid arthritis magnetic resonance imaging scoring.

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