Prevention of the progressive biochemical cartilage destruction under methotrexate therapy in early rheumatoid arthritis

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Abstract

Objective

The aim of the study was to investigate biochemical cartilage composition under methotrexate (MTX) therapy and to intra-individually assess the impact of inflammation severity on cartilage composition by using dGEMRIC MRI in patients with early rheumatoid arthritis (eRA).

Methods

dGEMRIC of MCP joints of the index and middle finger of 28 patients from the AthroMark cohort were examined prior to MTX-therapy as well as after 3 and 6 month. OMERACT RA MRI score and clinical parameters (CRP and DAS28) were registered at any time point. Each patient's second and third MCP joints were dichotomised into the joint with more severe synovitis versus the joint with less severe synovitis according to the RAMRIS synovitis subscore.

Results

MCP joints with more severe synovitis ('bad joints') demonstrated significantly lower dGEMRIC values compared to MCP joints with less severe synovitis ('good joints') at time-points 0 and 3 months (p=0.002; p=0.019, respectively). After 6 months of MTX therapy no significant difference of dGEMRIC index was found between good and bad joint (p=0.086).

Conclusion

Under MTX therapy, biochemical cartilage integrity remains stable; no further cartilage destruction occurred if patients were treated early in the course of the disease. In addition, six months of MTX therapy triggered an alignment of dGEMRIC index of MCP joints with initially severe synovitis and less severe synovitis in an intra-individual assessment. This underlines the importance of an early treatment in eRA to reduce further cartilage damage of the inflamed joints.

Key words

magnetic resonance imaging, dGEMRIC, early rheumatoid arthritis, methotrexate therapy

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Introduction

Rheumatoid arthritis (RA) is characterised by inflammation of the synovia that can result in progressive joint destruction resulting in long-term functional disability (1, 2). The extent of inflammation of the synovial membrane correlates with joint destruction and functional impairment (3-5). This implies the importance of early treatment in RA reaching remission of the inflammatory joint disease achieved by therapy guidelines and recommendations of the American College of Rheumatology and the European League Against Rheumatism that recommend all patients diagnosed with RA should be treated with conventional synthetic disease-modifying drugs, ideally before erosive disease will be detected (6, 7). Although patients contemporary gave the diagnosis RA and treated by the existing guidelines, some show erosive progression of the disease (1, 8). This has put magnetic resonance imaging (MRI) of bony and cartilage damage in the focus of monitoring RA. In 2003, the Outcome Measures in RA Clinical Trials group with the RA MRI Score (RAMRIS) established a highly reliable sum-score based on the semi-quantitative rating of the severity of synovitis, bone marrow oedema and erosions in hand and wrist joints that has been applied in therapy-response trials in RA (9, 10). However, cartilage destruction has not been quantified with RAMRIS. This is all the more relevant in view of the study of Aletaha *et al*. who demonstrated that physical disability in RA is associated with cartilage damage rather than bone destruction (11). Delayed gadolinium-enhanced MRI of the cartilage (dGEMRIC) is a highly reliable, histologically controlled MRI feature to visualise proteoglycan loss in cartilage composition (12-15). With dGEMRIC, it is possible to detect proteoglycan loss after the intravenous application of negatively charged contrast agent (gadolinium diethylenetriamine pentaacetate anion – Gd-DTPA). The negatively charged Gd-DTPA penetrates cartilage in an inverse relationship to the concentration of negatively charged glycosaminoglycan side chains of proteoglycan. A depletion of proteoglycan content in degenerated cartilage results in an accumulation of the paramagnetic gadolinium ions (16, 17). This consecutively accelerates T1 relaxation time (18). Even in early RA (eRA), molecular cartilage damage could be found in this early stage of the disease while morphological alterations are not visible (19, 20). We know that structural bony destructions develop mostly at bare area, an area without cartilage coat. This protection is at stake in progressive disease and may lead to severe joint destruction. Additionally, McGonagle *et al*. found erosion formation which may not necessarily depend on the presence of a bare area (21). They found lesser bone destruction at these areas, so they conclude that cartilage coat minimise bone damage. However, cartilage damage is an important part of the disease progression in RA, and studies assessing joint space narrowing on conventional radiography have shown that joint space narrowing is independently associated with functional impairment and decreased work ability (22). The IMAGINE-RA trial showed the benefits using MR-guiding treatment in RA (23). According to the European League Against Rheumatism recommendations, therapy with methotrexate (MTX) is the anchor of the treatment management in early RA (24). The aim of our study was to investigate biochemical cartilage composition under MTX therapy and to intra-individually assess the association of inflammation severity and cartilage integrity by using dGEMRIC in patients with eRA. Our hypothesis was that MTX halts molecular cartilage degradation over time.

Material and methods

Study population

Our study was approved by two local ethics committees (study number 3828; request number EA1/193/10). Informed consent was obtained from all individual participants included in the study. Metacarpophalangeal joints of the index finger (MCP2) and the middle finger (MCP3) of 28 patients with eRA (disease duration ≤6month, Ø 16.3 weeks; min. 2 weeks, max. 23 weeks) fulfilling the ACR/EULAR 2010 criteria from the ArthroMark study cohort

Table I.

Sequence/ parameter	STIR without contrast agent	T1w-TSE without contrast agent	3 D-FLASH without contrast agent	TSE with contrast agent	SE with contrast agent	3D-FLASH with contrast agent
Orientation	coronal	coronal	coronal	coronal	transversal	Sagittal
TE/TR (ms/ms)	31 / 5560	25/ 860	1.44/ 15	25/ 120	12/ 765	3.34 / 15
Flip angle (°)	120	150	5 and 26	150	90 and 120	5 and 26
Slice thickness (mm)	2.5	2.5	3	2.5	2.5	2.0
Field of view FOV (mm x mm)	120 x 120	120 x 120	160 x 160	120 x 120	120 x 60	90 x 53.5
Number of acquired slices	17	17	14	17	17	22
Time interval between two acquisitions	-	-	-	-	-	-
Number of images	1	1	2	1	1	2

(mean age: 56.8 years; min. 39 years, max. 74 years; 18 females; 10 males) were enrolled in this prospective study, examined at a 3T MRI system (Magnetom Trio A Tim System; Siemens Healthcare, Erlangen, Germany) of the clinically dominant hand (hand with more pain and swollen joints compared to the other hand, scored by rheumatologist (25)). MRI was performed at baseline (prior to therapy) and three and six months after starting of MTX therapy. RAMRIS, including synovitis, oedema and erosion subscores, and clinical parameters (CRP and DAS28) were registered at all time points (26).

MR protocol

MRI was performed of the dominantly affected hand on a 3T MRI system (Magnetom Trio; Siemens Healthcare). Subjects were imaged in a prone position with the hand extended over the head. For anatomical imaging, a coronal short tau inversion recovery (STIR) sequence, T1-weighted turbo spin echo (TSE) sequence and two 3D fast low angle shot (3D-FLASH) sequences using two different flip angles for T1-mapping were acquired before injection of contrast agent. After contrast agent injection, a coronal TSE and a transversal SE-sequence with fat suppression were applied. Sequence parameters were chosen accordingly to a previous study (20) and are listed in Table I. Gadolinium-MRI contrast agent was applied intravenously (0.4 ml/kg body weight of Gd-DTPA2-, Magnevist; Schering). Biochemical MRI with dGEMRIC of the MCP joints of the index and middle fingers was performed with two 4-cm loop surface coils placed above and beneath the MCP joint. The size of the coils and the FOV limited the examination to two adjacent joints: MCP 2 and 3. dGEMRIC was acquired 40 min after contrast agent administration (17). Variable flip-angle three-dimensional gradient-echo imaging (with two flip angles) was used for T1calculation (17). Flip angles were set to 5° and 26°. Twenty-two sagittal slices with a thickness of 2mm were positioned perpendicular to the joint spaces. The matrix of 312×384 provided an in-plane resolution of 233 μm. Total acquisition time was 2.25 min. To reduce movement artefacts, motion correction was performed on each patient's MCP joint before image analysis using STROKETOOL (Frechen, Germany) (27).

Image analysis

MR images were analysed according to RAMRIS in consensus by two radiologists trained in musculoskeletal imaging to assess synovitis subscore (range 0–3), especially of MCP 2 and 3. The two readers were blinded to patients' data and dGEMRIC values. In the cases of identical RAMRIS synovitis subscores in MCP 2 and 3, a subjective gradation into the joint with more severe synovitis and the joint with less severe synovitis was undertaken by the two radiologists in consensus. Based on this data, the RAMRIS synovitis subscore of second and third MCP, each patient's pair of MCP2 and MCP3 was dichotomised into the joint with more severe synovitis *versus* the joint with less severe synovitis ('bad joint *vs*. good joint') according to a prior study of our working group (19). Molecular imaging with dGEMRIC was performed of second and third MCP. To determine cartilage quality, T1 maps were analysed using region of interest (ROI) measurements. T1 values were calculated pixelwise. Gradient-echo images with a flip angle of 5° were used as anatomic reference for cartilage identification, and ROIs were set in the phalangeal and metacarpal cartilage of the MCP joints of the index and middle fingers. The ROIs were transferred to the co-registered T1 map. The dGEMRIC index in ms was recorded.

Statistical analysis

Statistical analysis was performed using MATLAB (MathWorks, Natick, MA, R2015a). The mean, 95% confidence intervals for the mean values,

Table II.

D2 Index Finger (ms)	General			Low synovitis ('good joints')			High synovitis ('bad joints')		
	T0	T3	T6	T0	T3	T6	T0	T3	T6
Mean	344.07	361.11	367.23	381.38	396.63	393.74	324.90	376.33	359.45
Std.	78.32	79.88	69.73	74.56	73.48	50.43	96.44	111.81	64.08
Min.	250.78	189.46	192.28	290.70	304.27	320.51	212.05	217.92	282.14
Max.	514.22	528.97	505.29	493.08	528.97	439.21	520.07	566.64	477.87
Lower Limit	310.57	326.95	337.41	326.14	342.20	356.38	253.46	293.50	311.98
Upper Limit	377.57	395.28	397.05	436.61	451.07	431.10	396.35	459.16	406.92
Median	331.46	354.53	379.49	391.70	409.97	422.42	296.42	381.97	352.61

Table III.

D3 Middel Finger (ms)	General			Low synovitis ('good joints')			High synovitis ('bad joints')		
	T0	T3	T6	T0	T3	T6	T0	T3	T6
Mean	400.65	423.76	392.71	438.52	447.48	409.34	325.41	343.35	353.98
StD.	110.82	129.33	82.69	99.84	134.70	87.93	75.80	79.40	75.75
Min.	212.05	217.92	244.54	280.90	226.08	244.54	250.78	189.46	192.28
Max.	577.00	724.20	556.74	576.98	724.20	556.74	514.22	448.56	505.29
Lower limit X	353.25	368.44	357.34	386.23	376.92	363.28	285.70	301.76	314.30
Upper limit X	448.05	479.07	428.08	490.82	518.04	455.40	365.12	384.95	393.66
Median (X)	372.39	392.31	364.52	444.83	443.96	405.51	303.50	343.14	371.89

median and standard deviations for dGEMRIC indices were calculated as descriptive statistics (listed in Tables II-IV).

Kolmogorow-Smirnow-Lilliefors tests were used for testing normal distribution. Mann-Whitney U-test (for non-normally distributed data) was applied to show the differences of cartilage composition with the dGEMRIC index of second and third MCP joints between the different time points before and after the initiation of MTX therapy. Wilcoxon paired rank sum test for dichotomous analysis was applied to compare dGEMRIC index of the MCP joints with more severe synovitis ('bad joints') and less severe synovitis ('good joints') to illustrate if parameters are significant different at the different time points (0, 3 and 6 months). *p*-values below 0.05 were considered to be significant.

Results

Descriptive analysis of dGEMRIC index in milliseconds (mean, standard deviation, median minimum, maximum, upper and lower limit of the 95% confidence interval) for MCP 2 and 3, as well as separated into low synovitis ('good joints) and high synovitis ('bad joints'), at the three different time points (T0 = baseline MRI before MTX treatment; T3 = three months, T6 = six months after beginning of MTX therapy) are summarised in Tables II-IV.

Additionally RAMRIS synovitis subscore demonstrated a decrease after three months of MTX therapy on MCP 2 (T0: 2.5; T3 2.0) and MCP 3 level (T0: 2.36; T3 2.04). Further, there also was a decrease in the RAMRIS oedema subscore on MCP 3 level after three and six months (T0: 0.43; T3: 0.29; T6: 0.29).

Table IV.

Total D2+D3	Low synovitis			High synovitis		
	T0	T3	T6	T0	T3	T6
Mean	400.65	423.76	392.71	344.07	361.11	367.23
Std.	110.82	129.33	82.69	78.32	79.88	69.73
Min.	212.05	217.92	244.54	250.78	189.46	192.28
Max.	576.98	724.20	556.74	514.22	528.98	505.29
Lower Limit	353.25	368.44	357.34	310.57	326.95	337.41
Upper Limit	448.05	479.07	428.08	377.57	395.28	397.05
median	372.39	392.31	364.52	331.46	354.53	379.49

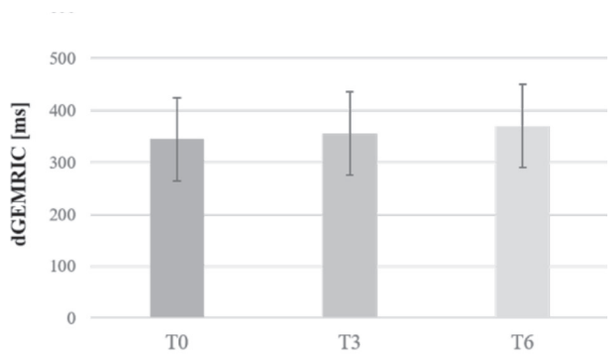

Fig. 1. dGEMRIC index in ms of MCP D2 of the different time points (from left to the right: T0, T3 and T6).
No significant difference was found between the different time points.

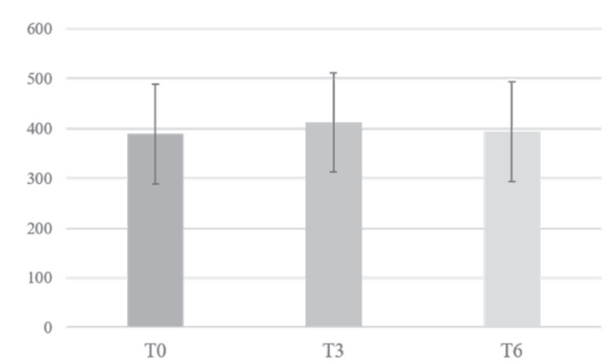

Fig. 2. dGEMRIC index in ms of MCP D3 of the different time points (from left to the right: T0, T3 and T6).
No significant difference could be revealed between the different time points.

Biochemical integrity of MCP joint cartilage under MTX therapy

dGEMRIC index of second and third MCP joint showed no significant difference between T0 and T3 (D2: p=0.45; D3: p=0.55) and between T0 and T6 (D2: p=0.15; D3: p=0.42) (Fig. 1-3).

Cartilage assessment of lower synovitis ('bad') vs. higher synovitis ('good') in MCP joints 2 and 3 in T0, T3 and T6

MCP joints with more severe synovitis ('bad joints') demonstrated significantly lower dGEMRIC values compared to MCP joints with less severe synovitis ('good joints') at time-point 0 and 3 months (p=0.002; p=0.019, respectively). After 6 months of MTX therapy, no significant difference of dGEMRIC index was found between good and bad joints (p=0.086) (Fig. 4-5). RAMRIS

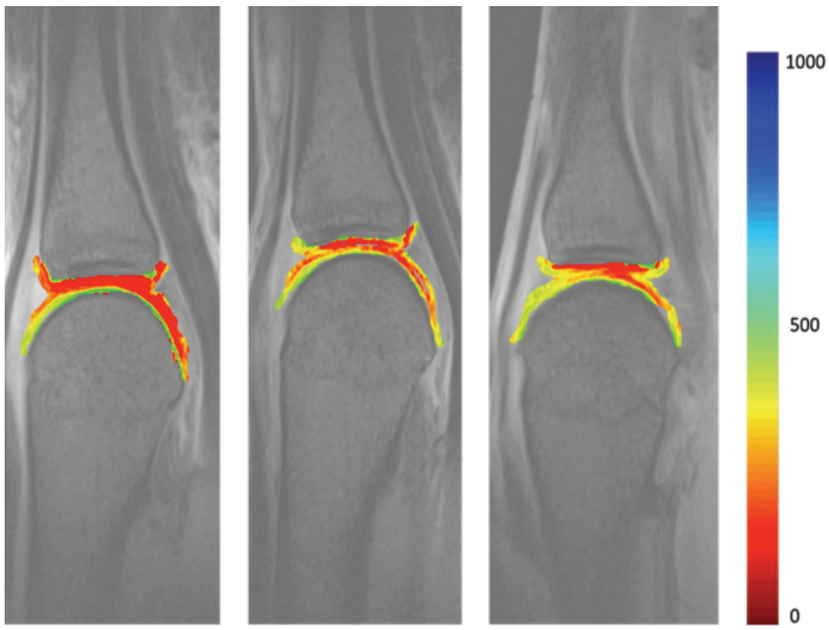

Fig. 3. Colour-coded dGEMRIC map with low dGEMRIC index in red and high dGEMRIC index in blue in ms. In this patient with high synovitis subscore (grade 3), no significant progression of cartilage damage could be illustrated. In contrast, subtle higher dGEMRIC index in T6 could be displayed.

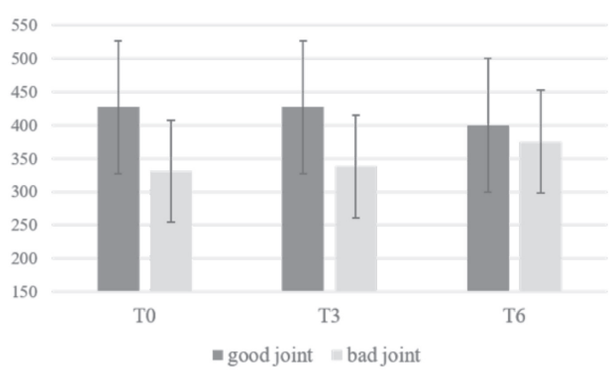

Fig. 4. 'Bad joints' showed significantly lower dGEMRIC index compared to 'good joints' at baseline measurements and three months after MTX therapy. Six months after the initiation of MTX therapy, no significant difference between 'bad and good joints' could be found.

synovitis subscore showed significantly higher scores in 'bad' *versus* 'good' joints (p=0.02; 2.64 *vs*. 2.18).

Discussion

Treat-to-target strategies are key concepts in current RA therapy management by which achieving remission or at least low disease activity via a rapid diagnosis combined with the use of csDMARDs, like MTX, is possible in the majority of patients (28-31). Subclinical inflammation in RA as a possible trigger for progressive joint destruction was reported and puts preservation of joint integrity into focus of therapy (1, 8). Our results revealed a stop of cartilage degradation under MTX therapy in a six months follow up. Herz *et al*. investigated the relation between inflammation of synovia and cartilage degradation measured with biochemical and morphological MRI (32). They demonstrated an association with high synovitis and proteoglycan loss measured by dGEMRIC.

A depletion of the proteoglycan content in the inflamed cartilage leads to an increased accumulation of contrast medium and an accelerated T1 relaxation time that can be detected with dGEMRIC (13, 19). In this context, joints with a higher RAMRIS synovitis subscore demonstrated significantly lower dGEMRIC values in an intraindividual analysis. To diminish confounders between subjects such as disease duration, age, gender, or therapy effects, we compared particular pair of adjacent joints in each patient (19). Our follow up study displayed higher cartilage destruction in joints with higher synovitis subscore ('bad joints') compared to joints with lower synovitis subscore ('good joints') at baseline and three months after start of MTX therapy. Six months after initiation of MTX therapy, we found an alignment between the proteoglycan loss of the previously 'bad and good joints'. Our results support the concept that inflammatory severity is associated with cartilage damage on a single joint level and can be stopped with antirheumatic therapy. In MCP D2, dGEMRIC indices increased over time. This may be a healing effect of the cartilage with higher proteoglycan content after the initiation of therapy. This effect was already described in knee joints after exercise (33). In RA, this effect was not described yet. In our study, the dGEMRIC increase was not significant, so it is possible that artefacts of molecular imaging lead to the increase. We had no histological confirmation about this.

Our study has limitations. One limitation was the small number of patients investigated in this study. This was partly due to the strict requirements of this study including only patients with early RA which were investigated at three time points. Further longitudinal studies are needed to confirm our results. No synovial and cartilage biopsies for histological analysis as a gold standard in evaluation of joint inflammation were available. Only few studies prepared synovial biopsies as gold standard (15). However, RAMRIS synovitis sub-score and dGEMRIC are well established methods to assess synovial inflammation (34) and cartilage damage (35). Additionally, the dGEMRIC values vary among different studies and protocols (32). The lack of a standard protocol for biochemical cartilage imaging limits the comparability of dGEMRIC between individual studies. Additionally, there is major overlap when comparing the different groups and dGEMRIC indices. This has to be taken into account when interpreting the results.

In conclusion, under MTX therapy, biochemical cartilage integrity remains stable, no further cartilage destruction occurred in the six month follow up. This might be explainable through reduced inflammation on joint level. In

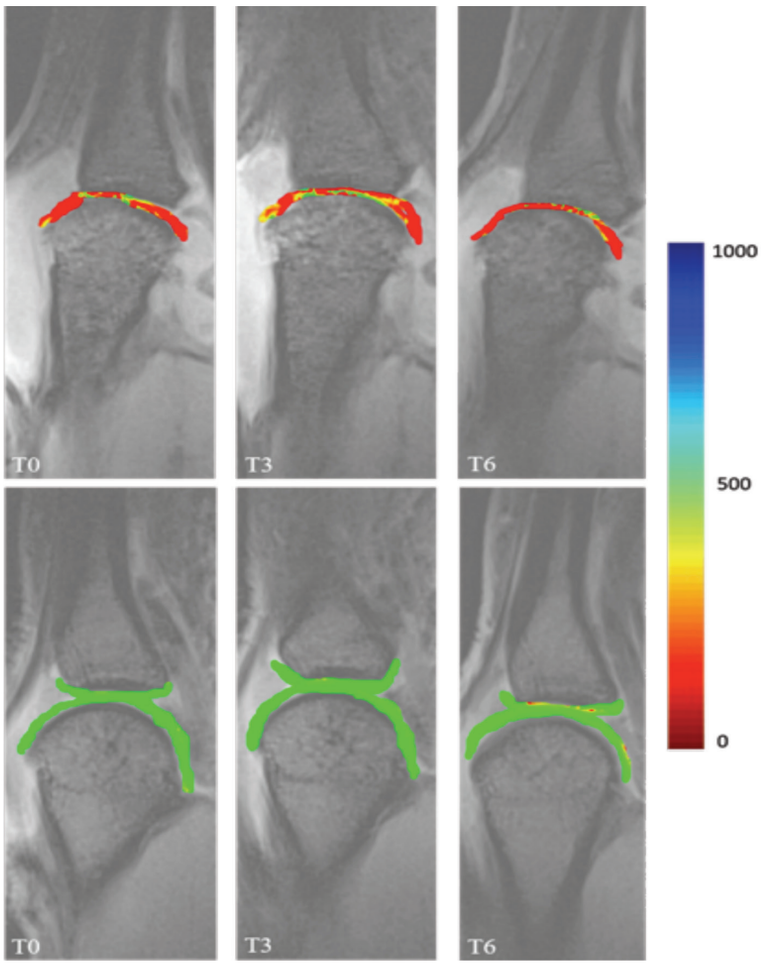

Fig. 5. Colour-coded dGEMRIC map with low dGEMRIC index in red and high dGEMRIC index in blue in ms. In this patient MCP joints with high synovitis subscore constantly demonstrated low dGEMRIC index across the different time points ('bad joint', upper row) compared to the 'good joint' (lower row).

addition, six months of MTX therapy triggered an alignment of dGEMRIC index of MCP joints with initially severe synovitis and less severe synovitis in an intra-individual assessment. This underlines the importance of an early treatment in eRA to reduce further cartilage damage of the inflamed joints. dGEMRIC may be an important tool to detect early molecular damage of cartilage in RA.

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