EXTENDED REPORT

Magnetic resonance imaging assessed inflammation in the wrist is associated with patient-reported physical impairment, global assessment of disease activity and pain in early rheumatoid arthritis: longitudinal results from two randomised controlled trials

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ABSTRACT

Objectives To examine whether MRI assessed inflammation and damage in the wrist of patients with early rheumatoid arthritis (RA) are associated with patient-reported outcomes (PROs).

Methods Wrist and hand MRIs of 210 patients with early RA from two investigator-initiated, randomised controlled studies (CIMESTRA/OPERA) were assessed according to the Outcome Measures in Rheumatology RA MRI score (RAMRIS) for synovitis, tenosynovitis, osteitis, bone erosions and joint space narrowing (JSN) at baseline, 1 and 5 years follow-up. These features, and changes therein, were assessed for associations with health assessment questionnaires (HAQ), patient global visual analogue scales (VAS-PtGlobal) and VAS-pain using Spearman's correlations, generalised estimating equations and univariate/multivariable linear regression analyses. MRI features were further tested for trends against specific hand-related HAQ items using Jonckheere trend tests.

Results MRI inflammation, but not damage, showed statistically significant associations with HAQ, VAS-PtGlobal and VAS-pain for status and change scores, independently of C reactive protein and swollen joint count. MRI-assessed synovitis was most consistently associated with PROs, particularly VAS-PtGlobal and VAS-pain. MRI-assessed synovitis and tenosynovitis mean scores were positively associated with patient-reported difficulty to cut meat and open a milk carton ($p<0.01$), and similar patterns were seen for other hand-related HAQ items. Incorporating metacarpophalangeal joints in the analyses did not strengthen the associations between MRI pathology and PROs.

Conclusions MRI-assessed inflammation, but not damage, in early RA wrists is associated with patient-reported physical impairment, global assessment of disease activity and pain and influences the physical function in the hand.

Trial registration number NCT00660647.

INTRODUCTION

Patient-reported outcomes (PROs) are widely used in rheumatoid arthritis (RA) to assess the patients' evaluation of how the disease affects physical function, pain and global assessment of disease activity.

Little is known about the relationships between PROs and different pathological findings in the joint, such as inflammation and structural damage. Studies in established RA have shown that radiographic progression is associated with increasing health assessment questionnaire (HAQ)-score over time. However, most studies have failed to document this association in the early stage of the disease.[1 2] MRI can detect bone erosions earlier in the disease course and with higher sensitivity than conventional radiography.[3–5] MRI can also visualise joint space narrowing (JSN),[6] and soft tissue pathologies, including synovitis, tenosynovitis and osteitis.[5 7] Thereby, it seems plausible that MRI findings might shed more light than conventional radiography on the pathological processes underlying the PROs. The association between MRI features and PROs has previously been addressed longitudinally in an established RA cohort,[8] and cross-sectionally in early RA cohorts.[9 10]

In a post hoc analysis of pooled data from two randomised placebo-controlled trials of patients with early RA, we aimed to examine whether MRI-assessed inflammation and damage in the early RA wrist are associated with physical function, global assessment of disease activity and pain at initiation of treatment and after 1 and 5 years' follow-up.

MATERIALS AND METHODS

Primary studies

The patients assessed in this post hoc analysis participated in the investigator-initiated, multicentre, randomised, double-blind, parallel-group, placebo-controlled CIclosporin, Methotrexate, Steroid in

RA (CIMESTRA) or OPtimised treatment algorithm in Early RA (OPERA) studies. These studies aimed at achieving inflammatory control by use of conventional and/or biological disease-modifying antirheumatic drugs (DMARDs) combined with intra-articular injection of glucocorticoids, and have been described in detail previously.[11 12] All patients had RA according to the 1987 American College of Rheumatology (ACR) criteria, disease duration <6 months and were DMARD-naïve. In both studies, one treatment arm received methotrexate plus intra-articular glucocorticoids, while the other arm received additional ciclosporin (CIMESTRA) or adalimumab (OPERA). Glucocorticoid injections were performed after obtaining MRIs and completing questionnaires. MRI was performed in 129 of 160 patients in CIMESTRA and 85 of 180 patients in OPERA.

In both studies, 28 tender and swollen joint counts (TJC/SJC) and C reactive protein (CRP) were obtained at each visit. Furthermore, the patients completed HAQ and assessment of patient global and pain visual analogue scales (VAS-PtGlobal and VAS-pain). In this post hoc analysis, 125 patients from the CIMESTRA study (4 patients excluded due to missing clinical data) and 85 patients from the OPERA study were included.

MAGNETIC RESONANCE IMAGING

MRIs were obtained of the non-dominant (CIMESTRA) or right (OPERA) wrist and, if the field of view allowed, the second-fifth metacarpophalangeal (MCP) joints at baseline (CIMESTRA/OPERA, n=210), 1 year (CIMESTRA/OPERA, n=206) and 5 years (CIMESTRA, n=113) visits. T1-weighted sequences (either isometric three-dimensional sequences, allowing multiplanar reconstruction, or axial+coronal two-dimensional sequences) before and after injection of intravenous contrast and coronal short-tau inversion recovery sequences were obtained. Information on MRI units and imaging parameters has previously been published.[13 14]

MRIs were assessed chronologically by one experienced reader, blinded to patient data. The image-sets were scored for synovitis (0–3), osteitis (0–3) and bone erosions (0–10) according to the Outcome Measures in Rheumatology (OMERACT) RA MRI score (RAMRIS)[5] and for tenosynovitis (0–3) and JSN (0–4) according to recently published OMERACT scoring systems.[7 15] As an intrareader analysis, baseline and follow-up images of 37 patients were reanonymised and reread (see online supplementary table S1).

Conventional radiography

Radiographs of both hands and forefeet were assessed chronologically for bone erosions and JSN at baseline, 1-year and 5 years follow-up by a reader blinded to patient data, using the Sharp van der Heijde (SvH) method.[16]

Statistics

The data from the patients in the CIMESTRA and OPERA studies were pooled and analysed as a single cohort. Clinical and biochemical data, SvH-scores and PROs were analysed as observed. The MRI scores were summarised to wrist scores, MCP scores and total scores. The wrist score was used as the primary analysis since this joint region was covered by the largest number of MRIs (table 1). MCP scores and total scores were assessed in additional analyses. The scores were also combined to inflammation scores (synovitis+tenosynovitis+osteitis) and damage scores (bone erosion+JSN). Data imputations of MRI scores were only allowed when ≥70% of the data points within a parameter (eg, 70% of the tendons at wrist level for scoring tenosynovitis) at an individual time point was available. Hence, completely missing MRI data at a time point were not imputed. Data were imputed using last observation carried forward and backward for missing follow-up and baseline data, respectively, in subjects with only one time point observed. In subjects with two time points observed, linear interpolation/extrapolation was used. If imputed values exceeded the maximum score or were negative, the maximum value and 0 was used, respectively. Of all data points included in the analyses, the following percentages were imputed: synovitis: 0.24%, tenosynovitis: 0.28%, osteitis: 0.58%, bone erosion: 0.54%, JSN: 0.16%.

Change between baseline and follow-up was assessed using the Wilcoxon signed-rank test. Clinical and MRI wrist baseline data were compared between the CIMESTRA and OPERA cohorts using the Mann-Whitney U test for continuous data and χ^2 test for nominal data. Status and change in MRI scores were explored for associations with HAQ-scores, VAS-pain and VAS-PtGlobal using Spearman's correlation analysis. Additionally, the association between MRI parameters and HAQ, VAS-pain and VAS-PtGlobal status and change scores was assessed over all time points using univariate generalised estimating equations (GEE), where variables with a p value ≤0.10 were included in multivariable models. SJC and CRP were also included in these models to assess relationships between MRI measures and PROs independent of clinical assessments. Change scores were further assessed in univariate linear regression models where independent variables with a p value ≤0.10 were included in multivariable regression models with backwards selection, where SJC and CRP were forced into the model. Log-transformation was applied to achieve normal distribution for status scores, and due to statistical skewness, the damage parameters were dichotomised for the GEE analyses at the median value for status scores as follows: JSN: 0/>0, erosion: ≤1/>1, combined damage score: ≤2/>2. For change scores, all damage parameters were dichotomised as 0/>0.

The association between MRI features and HAQ at baseline was further explored by calculating the mean of the different MRI scores for each HAQ increment in separate items hypothesised to involve the hand (the ability to cut meat, open a new milk carton, open previously opened jars, turn faucets on and off and lift a full cup or glass to the mouth). These groups were assessed for trends using the Jonckheere trend test.

SvH-scores were assessed for associations with HAQ, VAS-PtGlobal and VAS-pain using Spearman's correlation and univariate linear regression analyses.

A p value <0.05 was considered statistically significant. The statistical analyses were carried out using the SPSS V.22 (SPSS, Chicago, Illinois, USA) and STATA V.14 (StataCorp, College Station, Texas, USA).

RESULTS

Patient characteristics

At 1-year follow-up, the HAQ, VAS-pain and VAS-PtGlobal scores had improved markedly (p<0.01). Notably, the HAQ score did not change between 1 and 5 years follow-up, and the level of VAS-pain and VAS-PtGlobal changed minimally. All MRI wrist inflammatory scores showed a statistically significant decrease between baseline and both follow-up visits (except osteitis at 5 years follow-up), while MRI wrist damage scores showed a statistically significant increase (table 1). No

Table 1 Baseline and follow-up characteristics of the patients

	Baseline	1-year follow-up	5 years follow-up
Age	52 (13.6) n=210		
Sex, females, n (%)	138 (66%) n=210		
Disease duration, days	99 (44.8) n=210		
IgM RF positivity, n (%)	145 (69%) n=210		
Anti-CCP positivity, n (%)	133 (63%) n=210		
Tender joint count, range 0–28	11 (7) n=210	2 (5)* n=199	1 (4)* n=113
Swollen joint count, range 0–28	9 (6) n=210	1 (1)* n=199	1 (2)* n=113
VAS-pain, 0–100 mm VAS	49.9 (23.9) n=209	18.7 (20.7)* n=198	15.1 (20.9)* n=109
VAS-PtGlobal, 0–100 mm	53.6 (25.6) n=210	20.3 (22.4)* n=198	21.0 (1–23)* n=109
HAQ, range 0–3	1.1 (0.7) n=210	0.4 (0.5)* n=199	0.4 (0.5)* n=110
Serum CRP, mg/L	30.1 (33.5) n=207	11.2 (15.8)* n=198	6.6 (12.7)* n=112
DAS28 score, CRP based	5.3 (1.1) n=207	2.5 (1.1)* n=197	2.1 (1.1)* n=108
Total SvH score	5.2 (6.6) n=204	6.0 (7.4)* n=203	10.3 (13.2)* n=107
Erosive (SvH erosion score>0), n (%)	115 (56%) n=204	128 (63%) n=203	71 (66%) n=107
MRI parameters			
MRI wrist synovitis score, range 0–9	4.5 (2.4) n=198	3.1 (1.9)* n=186	2.6 (2.0)* n=92
MRI wrist tenosynovitis score, range 0–27	4.1 (4.2) n=194	1.4 (2.3)* n=187	0.8 (1.9)* n=92
MRI wrist osteitis score, range 0–45	2.5 (6.3) n=207	1.8 (5.7)* n=195	1.3 (3.7) n=94
MRI wrist erosion score, range 0–150	1.7 (2.4) n=205	2.2 (2.8)* n=194	3.0 (5.5)* n=95
MRI wrist JSN score, range 0–68	0.5 (1.3) n=209	0.8 (1.5)* n=195	1.6 (3.3)* n=94
MRI wrist combined inflammation score, range 0–81	11.2 (10.1) n=194	6.4 (7.5)* n=186	4.6 (5.7)* n=91
MRI wrist combined damage score, range 0–218	2.2 (3.2) n=205	2.9 (3.8)* n=194	4.6 (8.6)* n=94
Erosive wrist (RAMRIS erosion score>0), n (%)	127 (62%) n=205	130 (67%) n=194	72 (76%) n=95
MRI MCP synovitis score, range 0–12	4.3 (2.5) n=178	2.9 (2.0)* n=164	2.3 (2.1)* n=66
MRI MCP tenosynovitis score, range 0–12	2.4 (2.5) n=181	0.9 (1.7)* n=164	0.5 (1.1)* n=66
MRI MCP osteitis score, range 0–24	0.3 (1.0) n=182	0.2 (0.7)* n=175	0.1 (0.4) n=77
MRI MCP erosion score, range 0–80	0.8 (1.0) n=181	0.9 (1.2) n=169	0.9 (1.5)* n=72
MRI MCP JSN score, range 0–16	0.1 (0.5) n=173	0.1 (0.5)* n=173	0.1 (0.4) n=76
MRI MCP combined inflammation score, range 0–48	7.0 (4.5) n=164	4.0 (3.3)* n=156	2.9 (3.0)* n=64
MRI MCP combined damage score, range 0–96	0.9 (1.3) n=158	1.0 (1.4)* n=168	0.9 (1.7)* n=69
Erosive MCP joints (RAMRIS erosion score<0), n (%)	80 (44%) n=181	84 (50%) n=169	31 (43%) n=72
MRI total synovitis score, range 0–21	8.8 (4.1) n=173	5.9 (3.0)* n=162	4.6 (3.2)* n=66
MRI total tenosynovitis score, range 0–39	6.7 (6.0) n=172	2.2 (3.6)* n=163	1.0 (1.8)* n=66
MRI total osteitis score, range 0–69	2.9 (6.7) n=185	1.8 (5.4)* n=178	0.9 (3.1)* n=77
MRI total erosion score, range 0–230	2.5 (2.8) n=178	3.1 (3.3)* n=169	4.1 (6.3)* n=72
MRI total JSN score, range 0–84	0.6 (1.4) n=190	0.9 (1.7)* n=177	1.7 (3.6)* n=81
MRI total combined inflammation score, range 0–129	17.9 (12.8) n=156	9.7 (8.1)* n=156	6.6 (6.3)* n=64
MRI total combined damage score, range 0–314	3.1 (3.7) n=177	4.0 (4.3)* n=169	5.9 (9.9)* n=69
Erosive total scores (RAMRIS erosion score>0), n (%)	131 (74%) n=178	131 (78%) n=169	62 (86%) n=72

*p<0.05 (Wilcoxon signed-rank test) for comparison to baseline.
Mean (SD) scores of clinical, biochemical and MRI data at baseline and after 1-year and 5 years follow-up.
CCP, cyclic citrullinated protein; CRP, C reactive protein; DAS, disease activity score; HAQ, health assessment questionnaire; JSN, joint space narrowing; PtGlobal, patient global; RAMRIS, rheumatoid arthritis MRI score; RF, rheumatoid factor; VAS, visual analogue scale.

statistically significant difference was found between the CIMESTRA and OPERA cohorts at baseline, except disease duration (108 vs 84 days in CIMESTRA and OPERA, respectively), MRI-assessed tenosynovitis and combined inflammation score (data not shown).

Cross-sectional associations between MRI features and PROs

Statistically significant correlations were primarily seen between MRI synovitis, tenosynovitis and combined inflammation score and HAQ at baseline. MRI damage features only showed statistically significant correlations between JSN and HAQ at 1-year follow-up and between combined damage score and HAQ at 5 years follow-up (table 2). The univariate GEE analyses showed statistically significant associations for all inflammatory parameters and PROs, except osteitis versus VAS-pain. Osteitis demonstrated the strongest independent association with HAQ. For VAS-PtGlobal and VAS-pain, no independent associations were seen (table 3).

Associations between changes in MRI features and changes in PROs

Changes in MRI inflammatory features showed statistically significant correlations with changes in PROs from baseline to 1 and 5 years, except tenosynovitis versus HAQ between baseline and 5 years follow-up and tenosynovitis versus VAS-PtGlobal at all time intervals (table 2). In GEE models, changes in synovitis were associated with changes in VAS-pain and VAS-PtGlobal scores. The change in tenosynovitis and osteitis were associated

Table 2 Correlation between wrist MRI features and patient-reported outcomes

	Baseline	1-year follow-up	5 years follow-up	Δ Baseline – 1-year follow-up	Δ Baseline – 5 years follow-up
HAQ					
MRI synovitis	**0.25*** **	0.09	0.13	**0.21** **	**0.22***
MRI tenosynovitis	**0.18*** **	−0.02	0.13	**0.24** **	0.19
MRI osteitis	0.12	**0.21** **	0.18	**0.16***	**0.32** **
MRI erosion	0.03	0.08	0.16	0.00	−0.07
MRI JSN	−0.05	**0.19***	0.13	−0.08	−0.15
MRI combined inflammation	**0.21** **	0.08	0.16	**0.26** **	**0.25***
MRI combined damage	0.02	0.13	**0.21***	−0.02	−0.09
VAS-PtGlobal					
MRI synovitis	0.09	−0.01	0.02	**0.22** **	**0.32** **
MRI tenosynovitis	−0.01	−0.03	0.15	0.13	0.17
MRI osteitis	0.12	0.09	−0.02	**0.25** **	**0.24***
MRI erosion	−0.06	0.03	0.09	0.05	−0.09
MRI JSN	0.02	0.05	0.09	0.02	−0.16
MRI combined inflammation	0.07	0.03	0.04	**0.24** **	**0.30** **
MRI combined damage	−0.03	0.04	0.16	0.06	−0.14
VAS-pain					
MRI synovitis	**0.18***	0.03	−0.02	**0.28*** **	**0.45*** **
MRI tenosynovitis	0.04	−0.03	0.18	**0.16***	**0.29** **
MRI osteitis	0.08	0.14	−0.06	**0.22** **	**0.29** **
MRI erosion	−0.02	0.01	0.04	0.03	−0.18
MRI JSN	0.05	0.07	0.03	0.01	−0.16
MRI combined inflammation	0.11	0.08	0.01	**0.28*** **	**0.40*** **
MRI combined damage	0.00	0.03	0.08	0.03	−0.18

Associations for status and change scores by Spearman's correlations. Statistically significant correlations are written in bold and are interpreted as follows: *p<0.05, **p<0.01, ***p<0.001.
Δ, change; HAQ, health assessment questionnaire; JSN, joint space narrowing; PtGlobal, patient global; VAS, visual analogue scale.

with changes in HAQ. The change in combined inflammation scores was significantly associated with change in all PROs (table 3). Change in synovitis, tenosynovitis and combined inflammation showed statistically significant or borderline significant association with change in HAQ, VAS-PtGlobal and VAS-pain at all time intervals in the univariate regression models. The association of change in synovitis with PROs was independent of change in CRP and SJC at all time intervals, except for HAQ between baseline and 1 year. The association of change in combined inflammation score was independent of change in CRP and SJC between baseline and 5 years follow-up. Change in erosion, JSN and combined damage score showed no statistically significant associations with change in PROs in any analyses (table 4).

Baseline associations between MRI scores and single HAQ items

The mean synovitis and tenosynovitis scores increased with each increment of the HAQ scale for the items regarding ability to cut meat and open a milk carton (p<0.01). Similar patterns were seen for the other hand-related HAQ items. The association between the mean osteitis score and HAQ items showed a varying pattern (figure 1). Damage parameters showed no statistically significant trends for any items (data not shown).

Conventional radiography

Greater SvH-scores for bone erosion were correlated with lower VAS-pain at baseline (−0.14, p<0.05) and there was an inverse relationship in linear regression for change in JSN with change in VAS-PtGlobal from baseline to 5 years follow-up (−1.91, 95% CI −3.28 to −0.54, p=0.01). No other statistically significant associations were found between SvH-scores and PROs (data not shown).

Influence of including MCP joints in the analyses

Univariate and multivariable analyses of the MRI scores in the MCP joints showed fewer statistically significant independent associations with PROs for linear regression analyses but not for GEEs (see online supplementary Tables S2 and S3). Using total scores (wrist+MCP joints) showed the same pattern, as when using the wrist only (see online supplementary Tables S4 and S5). A sensitivity analysis was performed, in wrist MRIs, limited to patients having both joint regions scanned (ie, subjects with total scores). This analysis showed similar findings as the primary wrist group (see online supplementary Tables S6 and S7).

Sensitivity analyses

By analyses of correlations, regression analyses and GEEs using MRI data without imputations, no originally statistically significant results became non-significant, except for the correlation between 0–5 years change in synovitis and change in HAQ (see online supplementary Tables S8-S10).

DISCUSSION

This post hoc analysis of patients with early RA showed a statistically significant association between MRI synovitis, tenosynovitis and osteitis in the wrist and HAQ, VAS-PtGlobal and VAS-pain but not between MRI/radiographic bone erosion and JSN and PROs. Synovitis was most consistently associated with PROs, particularly VAS-PtGlobal and VAS-pain. This association seemed weaker for HAQ. However, hand function, as measured by HAQ was significantly associated with synovitis and

Table 3 Univariate and multivariable generalised estimating equations for wrist scores

	Status				Change			
	Univariate		Multivariable		Univariate		Multivariable	
	β (95% CI)	p Value	β (95% CI)	p Value	β (95% CI)	p Value	β (95% CI)	p Value
HAQ†								
MRI synovitis	0.06 (0.04 to 0.07)	**<0.001**	0.00 (−0.02 to 0.02)	0.97	0.08 (0.04 to 0.12)	**<0.001**	−0.01 (−0.04 to 0.03)	0.72
MRI tenosynovitis	0.04 (0.03 to 0.05)	**<0.001**	0.01 (0.00 to 0.02)	0.14	0.07 (0.04 to 0.09)	**<0.001**	0.02 (0.00 to 0.04)	**0.05**
MRI osteitis	0.01 (0.01 to 0.02)	**<0.001**	0.04 (0.00 to 0.01)	**0.03**	0.02 (0.01 to 0.04)	**0.001**	0.01 (0.00 to 0.02)	**0.04**
MRI erosion	−0.03 (−0.11 to 0.05)	0.51			0.08 (−0.09 to 0.26)	0.35		
MRI JSN	−0.02 (−0.09 to 0.06)	0.67			−0.02 (−0.25 to 0.21)	0.84		
MRI combined inflammation*	0.02 (0.01 to 0.02)	**<0.001**	0.00 (0.00 to 0.01)	0.16	0.03 (0.01 to 0.04)	**<0.001**	0.01 (0.00 to 0.02)	**0.01**
MRI combined damage*	−0.06 (−0.12 to 0.02)	0.16			0.07 (−0.11 to 0.24)	0.44		
VAS-PtGlobal†								
MRI synovitis	0.10 (0.08 to 0.13)	**<0.001**	0.01 (−0.02 to 0.04)	0.48	4.13 (2.55 to 5.71)	**<0.001**	1.79 (0.34 to 3.23)	**0.02**
MRI tenosynovitis	0.06 (0.05 to 0.07)	**<0.001**	0.01 (−0.01 to 0.02)	0.29	2.12 (1.14 to 3.09)	**<0.001**	−0.08 (−1.08 to 0.92)	0.88
MRI osteitis	0.01 (0.00 to 0.02)	**0.004**	0.00 (−0.01 to 0.01)	0.92	0.90 (0.22 to 1.58)	**0.01**	0.21 (−0.25 to 0.66)	0.37
MRI erosion	−0.09 (−0.20 to 0.02)	0.11			3.10 (−4.69 to 10.90)	0.44		
MRI JSN	−0.03 (−0.16 to 0.10)	0.65			−3.33 (−12.06 to 5.40)	0.46		
MRI combined inflammation*	0.02 (0.01 to 0.03)	**<0.001**	0.00 (0.00 to 0.01)	0.10	0.96 (0.48 to 1.44)	**<0.001**	0.42 (0.06 to 0.78)	**0.02**
MRI combined damage*	−0.09 (−0.20 to 0.02)	0.12			1.62 (−5.92 to 9.16)	0.67		
VAS-pain†								
MRI synovitis	0.09 (0.05 to 0.13)	**<0.001**	0.02 (−0.01 to 0.05)	0.14	4.64 (3.20 to 6.08)	**<0.001**	2.20 (0.87 to 3.53)	**0.001**
MRI tenosynovitis	0.05 (0.03 to 0.06)	**<0.001**	0.01 (−0.01 to 0.05)	0.19	2.19 (1.30 to 3.09)	**<0.001**	−0.02 (−0.91 to 0.87)	0.96
MRI osteitis	0.01 (0.00 to 0.02)	0.20			0.89 (0.21 to 1.57)	**0.01**	0.21 (−0.27 to 0.68)	0.39
MRI erosion	−0.06 (−0.17 to 0.05)	0.28			0.13 (−6.85 to 7.10)	0.97		
MRI JSN	0.01 (−0.10 to 0.12)	0.83			−1.24 (−9.09 to 6.61)	0.76		
MRI combined inflammation*	0.02 (0.01 to 0.02)	**<0.001**	0.00 (0.00 to 0.01)	0.16	1.02 (0.55 to 1.49)	**<0.001**	0.48 (0.11 to 0.85)	**0.01**
MRI combined damage*	−0.08 (−0.19 to 0.03)	0.15			−3.74 (−10.12 to 2.65)	0.25		

*If sum scores in univariate GEE had a p-value≤0.10, this was included in a separate multivariable GEE model with CRP and SJC.
†Log-transformed for status scores.
Association between MRI parameters and patient-reported outcomes for status scores and change scores. All generalised estimating equations (GEE) were adjusted for age and sex. MRI parameters with a univariate p≤0.10 were included in multivariable GEE analysis where CRP and SJC were incorporated.
HAQ, health assessment questionnaire; JSN, joint space narrowing; PtGlobal, patient global; VAS, visual analogue scale.

tenosynovitis at baseline. Incorporating MCP joints to the analyses did not improve the associations between MRI pathology and PROs.

This study is the first to document statistically significant associations between MRI inflammation and different PROs, and changes therein, in a longitudinal setting for patients with early RA. The association between MRI features and PROs has previously been described in different settings.[17] Ranganath *et al*[10] found a trend but non-significant association between MRI inflammation and HAQ in patients with RA in remission. Benton *et al*[18] reported that osteitis was the only single MRI parameter correlating with HAQ at baseline in patients with early RA. After 6 years, a statistically significant and borderline significant correlation with HAQ was found for bone erosion and tendinitis, respectively. The study was limited by small sample size (n=42). In a cross-sectional study, Burgers *et al*[9] showed that MRI-assessed synovitis, tenosynovitis and osteitis were associated with HAQ in univariate linear regression models in 514 patients with early, clinically confirmed arthritis. In multivariable regression analyses, tenosynovitis was associated

Table 4 Univariate and multivariable linear regression analyses for wrist scores

	Δ Baseline–1-year follow-up				Δ Baseline–5 years follow-up			
	Univariate		Multivariable		Univariate		Multivariable	
	β (95% CI)	p Value	β (95% CI)	p Value	β (95% CI)	p Value	β (95% CI)	p Value
HAQ								
ΔRI synovitis	0.06 (0.02 to 0.10)	**0.01**			0.09 (0.03 to 0.15)	**0.003**	0.07 (0.01 to 0.13)	**0.02**
ΔMRI tenosynovitis	0.04 (0.02 to 0.07)	**0.001**			0.04 (0.00 to 0.07)	**0.04**		
ΔMRI osteitis	0.02 (0.00 to 0.03)	**0.05**			0.02 (0.00 to 0.05)	0.10		
ΔMRI erosion	0.01 (–0.07 to 0.08)	0.85			–0.03 (–0.06 to 0.01)	0.11		
ΔJSN	–0.01 (–0.13;0.11)	0.84			–0.05 (–0.11 to 0.02)	0.16		
ΔSJC	0.03 (0.02 to 0.05)	**<0.00001**	0.02 (0.01 to 0.04)	**0.01**	0.04 (0.02 to 0.06)	**0.001**		
ΔCRP	0.01 (0.01 to 0.01)	**0.00002**	0.01 (0.01 to 0.01)	**<0.00001**	0.01 (0.00 to 0.01)	**0.001**	0.01 (0.00 to 0.01)	**0.02**
ΔMRI combined inflammation*	0.01 (0.00 to 0.02)	**0.01**			0.02 (0.01 to 0.04)	**0.01**	0.02 (0.00 to 0.04)	**0.02**
ΔMRI combined damage*	0.00 (–0.05;0.06)	0.93			–0.02 (–0.04 to 0.00)	0.11		
VAS-PtGlobal								
ΔMRI synovitis	3.08 (1.18 to 4.98)	**0.002**	2.53 (0.65 to 4.41)	**0.01**	4.56 (2.33 to 6.79)	**0.0001**	3.37 (0.95 to 5.79)	**0.01**
ΔMRI tenosynovitis	1.11 (0.02 to 2.21)	**0.05**			1.33 (0.01 to 2.65)	**0.05**		
ΔMRI osteitis	0.70 (0.02 to 1.39)	**0.05**			1.33 (0.43 to 2.23)	**0.004**		
ΔMRI erosion	–1.22 (–4.63;2.20)	0.50			–0.84 (–2.07 to 0.40)	0.18		
ΔMRI JSN	0.40 (–5.01;5.81)	0.89			–1.82 (–4.26 to 0.62)	0.14		
ΔSJC	0.83 (0.13 to 1.53)	**0.02**			1.94 (1.16 to 2.72)	**<0.00001**	1.29 (0.31 to 2.27)	**0.01**
ΔCRP	0.28 (0.15 to 0.38)	**0.00002**	0.22 (0.10 to 0.35)	**0.001**	0.22 (0.06 to 0.38)	**0.01**		
ΔMRI combined inflammation*	0.50 (0.04 to 0.96)	**0.03**			1.11 (0.54 to 1.67)	**0.0002**	0.78 (0.14 to 1.42)	**0.02**
ΔMRI combined damage*	–0.58 (–3.15;2.00)	0.66			–0.62 (–1.46 to 0.23)	0.15		
VAS-pain								
ΔMRI synovitis	3.54 (1.82 to 5.27)	**0.00008**	2.90 (1.20 to 4.61)	**0.001**	5.57 (3.52 to 7.61)	**<0.00001**	2.53 (0.22 to 4.84)	**0.03**
ΔMRI tenosynovitis	1.18 (0.18 to 2.18)	**0.02**			1.83 (0.58 to 3.09)	**0.01**		
ΔMRI osteitis	0.60 (–0.03;1.23)	0.06			1.49 (0.63 to 2.35)	**0.001**		
ΔMRI erosion	–1.94 (–5.03;1.15)	0.22			–1.12 (–2.31 to 0.07)	0.07		
ΔMRI JSN	1.92 (–3.32;7.17)	0.47			–1.51 (–3.89 to 0.87)	0.21		
ΔSJC	1.01 (0.38 to 1.63)	**0.001**			2.20 (1.52 to 2.89)	**<0.00001**	0.86 (–0.01;1.74)	**0.05**
ΔCRP	0.27 (0.16 to 0.37)	**<0.00001**	0.22 (0.10 to 0.33)	**0.0002**	0.40 (0.26 to 0.53)	**<0.00001**	0.26 (0.10 to 0.41)	**0.00**
ΔMRI combined inflammation*	0.52 (0.10 to 0.94)	**0.02**			1.33 (0.80 to 1.85)	**<0.00001**	0.96 (0.37 to 1.56)	**0.00**
ΔMRI combined damage*	–0.71 (–3.06;1.65)	0.55			–0.71 (–1.53 to 0.10)	0.09		

*If combined inflammation or damage scores in univariate regression analyses had a p value ≤0.10, this was included in a separate multivariable regression model with CRP and SJC.
Analyses for associations between the change of MRI features and change in patient-reported outcomes. All multivariable analyses were adjusted for sex and age. Statistically significant or borderline significant p values (≤0.05) are written in bold.
Δ, change; CRP, C reactive protein; HAQ, health assessment questionnaire; JSN, joint space narrowing; PtGlobal, patient global; SJC, swollen joint count; VAS, visual analogue scale.

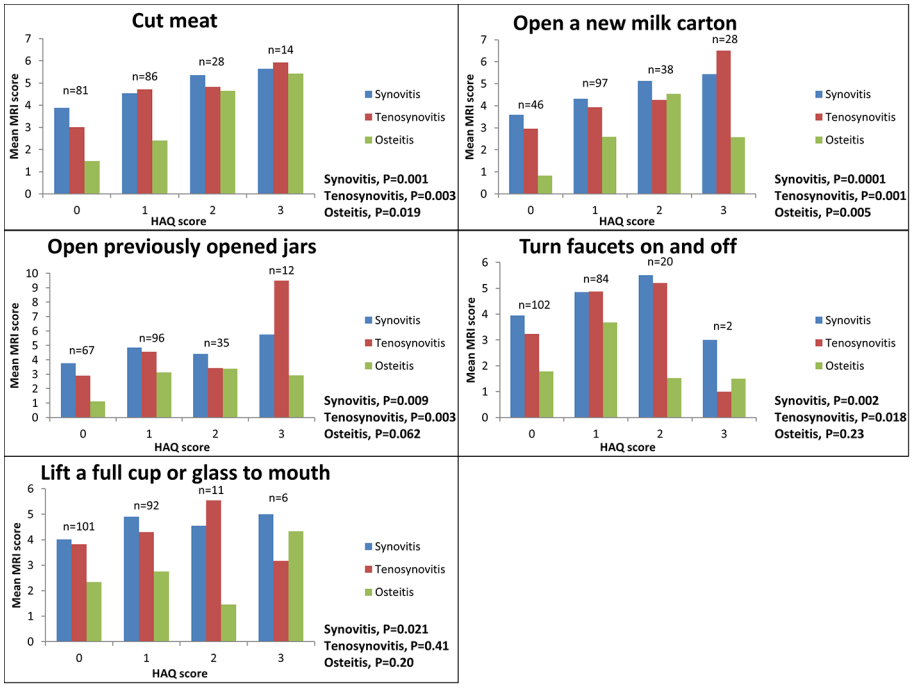

Figure 1 Mean inflammatory involvement distributed on specific hand-related HAQ items. The columns refer to the mean RAMRIS scores for the inflammatory features for each level of the hand-related HAQ item (x-axis). The HAQ scores are interpreted as follows: 0: no difficulty, 1: some difficulty, 2: much difficulty, 3: unable to perform the activity. n, number of patients; HAQ, health assessment questionnaire; RAMRIS, rheumatoid arthritis MRI score.

with HAQ, independently of clinical and biochemical measures. Bone erosion was not independently associated with HAQ. This pattern was also present in a subanalysis of 206 patients that fulfilled the European League Against Rheumatism/ACR 2010 criteria for RA at baseline. Furthermore, the group showed increasing amounts of synovitis and tenosynovitis with each score of hand-related HAQ items. The study did not assess JSN and the associations between MRI and HAQ were not studied in longitudinal settings. Baker *et al*[8] reported that MRI-assessed synovitis, osteitis and bone erosion were associated with HAQ, VAS-PtGlobal and VAS-pain at all time points between baseline and 1-year follow-up in a subset of 291 erosive methotrexate and biologic-naïve patients with RA from the GO-BEFORE study. Tenosynovitis and JSN were not assessed. Thus, previous and present data consistently support the importance of MRI-assessed inflammation for the patient experience in RA.

In our study, the multivariable linear regression analyses and GEE for change scores showed that change in MRI-assessed synovitis was consistently associated with changes in VAS-pain and VAS-PtGlobal. This association was also observed in the study by Baker *et al*.[8] These findings suggest that patients are prone to rate their global disease activity and pain higher with increasing amount of MRI-assessed synovitis in their wrists. Our analyses showed some associations between HAQ and synovitis, but also with tenosynovitis and osteitis. While Burgers *et al* found that MRI-assessed tenosynovitis had the strongest baseline associations with HAQ, our analyses showed a more variable pattern. The median combined wrist inflammation score was markedly lower in the cohort studied by Burgers *et al* (median 3.0 vs 11.2 in our cohort). A plausible cause to the different associations may be that lower amount of inflammation may contribute to variable relationships of synovitis, tenosynovitis, osteitis with HAQ. In agreement with our findings, Burgers *et al* found that the amount of tenosynovitis and synovitis in the wrist increased with higher level of disability in hand-related HAQ items at baseline.[9] We believe the results from our study support a connection between the local degree of inflammation in the wrist and impaired physical function of the hand.

Statistically significant association between radiographic damage and PROs was only seen between bone erosion and VAS-pain at baseline and between changes in JSN and VAS-PtGlobal between baseline and follow-up. These associations were, however, inverse and we therefore consider this a spurious finding.

The fact that the current study did not find an association between PROs and MRI/radiographic damage may be explained by the lower level of damage in the patients with early RA participating in the CIMESTRA and OPERA studies as compared with the GO-BEFORE subanalysis, where patients with RA were more erosive on radiographs and had longer disease duration (mean 1.2 years).[19] Indeed, the mean baseline total MRI bone erosion score was 14.5 in the study by Baker *et al* as compared with 2.5 in the CIMESTRA/OPERA cohort. Several studies have previously documented an association between radiographic damage and physical impairment.[2 20–22] However, in early RA the lack of substantial structural damage may result in a lack of influence of this disease feature on PROs compared with the inflammatory load. Interestingly, our results suggest that the influence of structural damage on PROs is minimal throughout at least 5 years of follow-up. In the current study, the PROs remained stable between 1 and 5 years follow-up. In the CIMESTRA and OPERA studies, a persistent treat-to-target strategy was applied to inflamed joints by aggressive use of intra-articular glucocorticoids and simultaneous escalation of disease-modifying treatment throughout the study.[11 12] This may explain why the change in structural damage was limited and not associated with change in PROs, after neither 1 nor 5 years follow-up.

In this post hoc analysis, we chose to use the wrist score as our primary analysis to achieve the largest sample size. Additional analyses showed that the assessment of the MCP joints provided little additional information. In general, comparing analyses of total scores (wrist+MCP scores) and wrist scores in the subset of patients with both wrist+MCP scores available gave similar results. Hence, MRI-assessed inflammation in the wrist rather than in the MCP joints seems to be most important for the physical function, pain and global assessment of disease activity in the patients with early RA. The MRIs were scored according to the RAMRIS, which includes the first carpometacarpal joint, but not the first MCP and interphalangeal joint. Including these joints could have provided further information on the association of thumb inflammation with the function of the hand. Hand osteoarthritis may coexist with RA and may influence PROs. However, bone damage did not show any significant associations with the PROs, suggesting that osteoarthritis had no major influence on our results.

Strengths of this post hoc analysis include the longitudinal setting and the large sample size, which allowed comprehensive analyses using linear regressions and GEE. Limitations include missing MRI data at different time points, although the range of missing MRIs was only 6%–8%, 3%–8% and 6%–9% for baseline, 1 year and 5 years, respectively. Furthermore, the results from 5 years follow-up are limited by the lower sample size. This study assessed associations between MRI features and PROs longitudinally in patients with early RA. Future studies should focus on assessing longitudinal associations in other cohorts, such as more advanced disease and RA in remission. Furthermore, the association between MRI features and designated measures of hand function should be investigated.[23]

In conclusion, MRI-assessed inflammation, but not damage, in early RA wrists is associated with patient-reported physical impairment, global assessment of disease activity and pain and the amount of wrist inflammation influences the level of physical function in the hand.

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