Arthritis Care & Research
Vol. 73, No. 11, November 2021, pp 1628–1637
DOI 10.1002/acr.24355

American College of Rheumatology
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Two-Year Changes in Magnetic Resonance Imaging Features and Pain in Thumb Base Osteoarthritis

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Objective. To investigate the two-year course of pain and osteoarthritic features on magnetic resonance imaging (MRI) in the thumb base.

Methods. Patients in the Hand Osteoarthritis in Secondary Care (HOSTAS) cohort who had received radiographic examination, MRI, and clinical examination of the right thumb base at baseline and who had a 2-year follow-up period were studied. Pain on palpation of the thumb base was assessed on a 0–3 scale. MRIs were analyzed with the Outcome Measures in Rheumatology (OMERACT) thumb base osteoarthritis MRI scoring system for synovitis, bone marrow lesions (BMLs), subchondral bone defects, cartilage space loss, osteophytes, and subluxation. Radiographs were assessed for osteophytes and joint space narrowing. We studied the associations of changes in synovitis and BMLs with changes in pain using a logistic regression model adjusted for radiographic damage, with values expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results. Of 165 patients, 83% were women and the mean age was 60.7 years. At baseline, 65 patients had thumb base pain. At 2-year follow-up, pain had decreased in 32 patients and increased in 33 patients. MRI features remained stable in most patients. Structural MRI features generally deteriorated, while synovitis and BMLs improved in some individuals and deteriorated in others. Change in radiographic osteophytes rarely occurred (n = 10). Increased synovitis (odds ratio [OR] 3.4 [95% CI 1.3–9.3]) and increased BMLs (OR 5.1 [95% CI 2.1–12.6]) were associated with increased pain. Decreased BMLs appeared to be associated with decreased pain (OR 2.7 [95% CI 0.8–8.9]), and reductions in synovitis occurred too infrequently to calculate associations.

Conclusion. Over 2 years, thumb base pain fluctuated, while MRI features changed in a minority of patients with hand osteoarthritis. Changes in synovitis and BMLs were associated with changes in pain on palpation, even after adjustment for radiographic damage.

INTRODUCTION

Hand osteoarthritis (OA) is a polyarticular disease, affecting the interphalangeal joints and the thumb base, a joint complex that includes the first carpometacarpal (CMC1) and scaphotrapeziotrapezoid (STT) joints. The thumb base has certain unique qualities, such as a high range of motion and the capability to bear high loads, which sets it apart from other hand joints (1–3). Thumb base OA is associated with different clinical and imaging outcomes than interphalangeal OA, and was therefore considered to be a separate hand OA subset (2–4). Most research in hand OA has focused on the hand as a whole or the interphalangeal joints specifically, and the 1990 American College of Rheumatology (ACR) classification criteria for OA of the hand (5) do not distinguish between interphalangeal OA and thumb base OA. Therefore, our knowledge of this hand OA subset and its natural course is limited.

Alongside structural joint damage, which is a hallmark of the disease, inflammatory features visible on magnetic resonance imaging (MRI), including synovitis and bone marrow lesions (BMLs), are often present in interphalangeal and thumb base OA (6–8). Cross-sectional studies have shown that in interphalangeal joints, synovitis and BMLs are associated with pain on palpation, and more strongly so than structural damage (6,7). Yet, in a study investigating these aspects in thumb base OA, the opposite was

Supported by the Dutch Arthritis Foundation (ReumaNederland) (grants 10-1-405 and LLP-24).

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Dr. Kloppenburg has received consulting fees on behalf of her institution from AbbVie, Pfizer, Levicept, GlaxoSmithKline, and Merck-Serono (less than $10,000 each) and has acted as a local investigator of an industry-driven trial conducted by AbbVie. No other disclosures relevant to this article were reported.

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Submitted for publication January 21, 2020; accepted in revised form June 9, 2020.

SIGNIFICANCE & INNOVATIONS

- In thumb base osteoarthritis (OA), the majority of patients have unchanged pain on palpation and unchanged magnetic resonance imaging (MRI) features after a 2-year follow-up.
- In patients who had changes on MRI during the follow-up period, structural osteoarthritic MRI features generally deteriorated, while synovitis and bone marrow lesions fluctuated.
- Change in MRI inflammation is associated with change in pain on palpation in thumb base OA.

seen—while synovitis and BMLs were associated with pain, structural damage was found to be the most important determinant of pain (8).

Longitudinal imaging studies of interphalangeal OA have shown that a change in MRI inflammation was also associated with a change in pain levels (9,10). In thumb base OA, however, no longitudinal imaging studies have been performed thus far. Hence, the natural course of osteoarthritic MRI features is unknown, as is the relation between changes in these features and clinical outcomes. Therefore, our aim was to investigate the two-year course of pain on palpation and MRI features in thumb base OA and their association with one another.

PATIENTS AND METHODS

Study design. We used longitudinal data from the Hand Osteoarthritis in Secondary Care (HOSTAS) study, an ongoing observational cohort of consecutive patients from our outpatient clinic who were included after being diagnosed with primary hand OA by their treating rheumatologist. Patients with secondary hand OA or with hand symptoms due to another cause were excluded. More details on patient recruitment and selection have been published elsewhere (11).

Participants with baseline and two-year follow-up data available were included in this analysis (Supplementary Figure 1, available on *the Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract). This study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee at Leiden University Medical Center. Written informed consent was obtained from all participants.

Demographic characteristics and clinical assessment. Demographic and clinical characteristics were collected with standardized questionnaires, including self-reported thumb base pain and stiffness during the last month (absent/present), the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) (12), and self-reported hand pain on a visual analog scale (VAS; range 0–100 millimeters). Trained research nurses examined the thumb base for pain upon palpation on a semiquantitative scale of 0–3 (13) and bony swelling (absent/present).

MRI acquisition and scoring. MRIs of the right CMC1 and STT joints were obtained at baseline and at two-year follow-up visits using an MSK Extreme 1.5T extremity MR imaging scanner (GE). The following sequences were acquired: coronal T1-weighted (T1) fast spin-echo (FSE) images with a repetition time (TR) of 575 msec and echo time (TE) of ≤11 msec, axial T1-weighted FSE images with a TR of 575 msec and a TE of ≤10.5 msec, coronal T2-weighted FSE images with frequency selective fat saturation and a TR of 3,000 msec and TE of 61.8 msec, and axial T2-weighted FSE fat saturation images with a TR of 3,000 msec and a TE of 60 msec. Eighteen coronal slices of 2-mm thickness with a slice gap of 0.2 mm and 20 axial slices of 3 mm-thickness with a slice gap of 0.3 mm were obtained. No intravenous contrast was administered.

Images were scored pairwise in chronological order by two readers (SvB and FPBK), who scored images independently while blinded in regard to clinical and radiographic data using the Outcome Measures in Rheumatology (OMERACT) thumb base osteoarthritis MRI scoring system (TOMS) (14–16). Synovitis, BMLs, subchondral bone defects (SBDs), cartilage space loss, and osteophytes were scored on a 0–3 scale for the CMC1 and STT joints, and CMC1 joint subluxation was scored dichotomously. Osteophytes, SBDs, and BMLs were scored for distal and proximal joint parts separately, adding up to a sum score of 6 (CMC1 joint) and 9 (STT joint). For changes in synovitis, half-point increments were used to indicate within-grade changes in SBDs and BMLs. Interrater reliability was moderate/good for all baseline features (mixed model, exact agreement, average measure intraclass correlation coefficients [ICCs] of 0.59–0.92 for a CMC1 joint subluxation prevalence-adjusted, bias-adjusted kappa [PABAK] of 0.77 [17]) and change scores (mixed model, exact agreement, average measure ICCs of 0.53–0.81 for a CMC1 joint subluxation PABAK of 0.88).

Radiograph acquisition and scoring. Posteroanterior hand radiographs were obtained at baseline and two-year follow-up. Images were scored in a paired chronological order by two readers (SvB and HMK) who scored in consensus while blinded in regard to clinical and MRI data. Osteophytes and joint space narrowing (JSN) in CMC1 (0–3 scale) and STT (absent/present) joints, and erosions and cysts in CMC1 joint (absent/present) were scored according to the Osteoarthritis Research Society International (OARSI) atlas (18). Intraobserver reliability based on a subset of 20 randomly selected patients was excellent (PABAK values of 0.8−0.9 for baseline and 0.9−1.0 for change scores).

Statistical analysis. A previous cross-sectional analysis of the associations between inflammatory MRI features, pain, and radiographic damage using baseline data of this cohort was performed as the starting point for the current study (8). To ascertain

that those findings also applied to the present study, which concerns a selection of the study population with follow-up data available in which different readers scored the radiographs (Supplementary Figure 1, available on *the Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract), we first repeated the cross-sectional analyses of associations between baseline synovitis, BMLs, and radiographic osteophytes (determinants) and presence of pain on palpation (outcome), adjusted for sex and body mass index. Next, using the difference between the change scores of the two independent readers, we determined the smallest detectable change as $\pm\ 1.96 \times SD_{\Delta(\text{CHANGE-SCORES})}/(\sqrt{2} \times \sqrt{k})$ with k = 2 (19) to use as a threshold for increases and decreases in MRI scores. All reported and analyzed MRI scores are based on the average of both readers. Since pain was assessed for the thumb base as a whole, change scores of the CMC1 and STT joints were combined, comparing no change in both joints (i.e., "stable") with an increase or decrease in at least one joint. A thumb base was also classified as "stable" when changes in one joint increased while changes in the other decreased. Radiographic baseline scores of the CMC1 and STT joints were combined and dichotomized similarly (absent in CMC1 and STT joints versus present in CMC1 or STT joints).

Using a logistic regression model, we then investigated the associations between imaging features (determinants) and change in pain on palpation (outcome), expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). First, we assessed whether baseline imaging features (synovitis, BMLs, or radiographic damage) were associated with increase in pain on palpation (excluding thumb bases with maximum pain at baseline) or decrease in pain on palpation (excluding thumb bases without pain at baseline) over two years (Supplementary Figure 2, available on *the Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract). Second, we assessed whether a 2-year increase in the imaging features (synovitis, BMLs, or radiographic damage) was associated with an increase in pain on palpation. For this, we excluded thumb bases with maximum score in the imaging feature or maximum pain at baseline (Supplementary Figure 2). Thumb bases with stable or decreased imaging features served as the reference category. Third, we examined a "reversed" situation for the MRI features, excluding thumb bases without synovitis or BMLs and without pain at baseline (Supplementary Figure 2). Thumb bases with stable or increased MRI features served as the reference category. All analyses were done in univariable and multivariable models, adjusted for other imaging features. Selection of covariates was based on proven or hypothesized associations with both the exposure and the outcome, which were then verified in our data set.

To explore possible interaction between structural damage and MRI features in relation to the course of pain, we also performed analyses assessing the association of increase in synovitis or BMLs with increased pain stratified for the presence or absence of baseline radiographic osteophytes. The attributable proportion was estimated, which reflects the proportion of the OR for the group who was exposed twice that was attributable to interaction (20,21). Since baseline radiographic osteophyte scores may not fully account for the structural damage in a joint, we performed two sets of sensitivity analyses in which we 1) replaced the osteophytes scores with JSN scores and 2) added JSN scores as an additional covariate to the models.

Data were analyzed using SPSS for Windows, version 23.0. Area Proportional Euler diagrams (Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract) were drawn using eulerAPE, version 3.0.0 (http://www.eulerdiagrams.org/eulerAPE/) (22).

RESULTS

Study population. In the HOSTAS cohort, 202 patients underwent MRI of the right thumb base at baseline, of whom 166 also underwent MRI of the same area at two-year follow-up (Supplementary Figure 1, available on *the Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract). One patient was excluded due to prior joint anatomy-altering thumb base surgery. The majority of the 165 patients included in the study fulfilled the ACR classification criteria for OA of the hand (5), were middle-aged, and female (Table 1). Baseline characteristics and imaging scores of patients included in the analyses were not different from those individuals who only underwent MRI at baseline.

Pain and imaging features at baseline. At baseline, 93 (56.4%) of the patients reported frequent pain in the right thumb base in the previous month, and 65 (39.4%) reported pain on palpation during physical examination, of whom 11 had maximum pain.

MRI features were highly prevalent at baseline, with a total of 81.6% of patients having at least one thumb base joint (CMC1 or STT) with synovitis or BMLs (Table 1). All MRI features were more prevalent in the CMC1 joint than in the STT joint. Generally, scores were low, which can be appreciated from the medians and interquartile ranges in Table 1. Osteophytes were the most frequently observed structural feature on MRI (86% of CMC1 joints and 52% of STT joints). Radiographic osteophytes were present in 74 thumb bases (45%), primarily in the CMC1 joints.

As expected, we reaffirmed previous findings (8) in this cohort that, cross-sectionally, pain on palpation was strongly associated with the presence of radiographic osteophytes (OR 7.4 [95% CI 3.47−15.7]), and that the association of inflammatory MRI features with pain (OR 3.05 [95% CI 1.35−6.9] for synovitis and OR 2.50 [95% CI 1.28−4.9] for BMLs) attenuated after adjustment for osteophytes (OR 1.63 [95% CI 0.66−4.0] for synovitis and OR 1.10 [95% CI 0.49−2.46] for BMLs).

Table 1. Baseline characteristics of 165 patients with hand OA*

	No. (%) or mean ± SD	Median (IQR)
Demographic characteristic		
Female sex	137 (83.0)	–
Age, years	60.7 ± 8.3	–
Fulfilment of ACR criteria for hand OA	151 (91.5)	–
Clinical assessment		
Body mass index, kg/m^2†	27.5 ± 5.1	–
VAS right hand pain, 0–100 mm scale	36 (21)	–
Self-reported pain of right thumb base	93 (56.4)	–
Self-reported stiffness of right thumb base	58 (35.2)	–
Presence of pain on palpation of right thumb base	65 (39.4)	–
Bony swelling of right thumb base	74 (44.8)	–
AUSCAN hand pain, 0–20 scale	–	10 (6–12)
AUSCAN hand physical function, 0–36 scale	–	16 (10–22)
Self-reported use of acetaminophen	85 (51.5)	–
Self-reported use of NSAIDs	50 (30.3)	–
Self-reported use of thumb base splint	11 (6.7)	–
Radiography of the right hand‡		
CMC1 joint		
Presence of OARSI osteophytes	74 (45.1)	–
Presence of OARSI joint space narrowing	61 (37.2)	–
STT joint		
Presence of OARSI osteophytes	9 (5.5)	–
Presence of OARSI joint space narrowing	32 (19.5)	–
MR imaging of the right hand		
CMC1 joint		
Presence of synovitis§	69 (42.3)	–
Synovitis, 0–3 scale§		0 (0–1)
Bone marrow lesions, 0–6 scale§	79 (48.5)	0 (0–2)
Subchondral bone defects, 0–6 scale	95 (57.6)	1 (0–1)
Cartilage space loss, 0–3 scale	81 (49.1)	0 (0–1)
Osteophytes, 0–6 scale	141 (85.5)	2 (1–4)
Presence of subluxation	30 (18.2)	–
STT joint		
Presence of synovitis§	65 (39.9)	–
Synovitis, 0–3 scale§		0 (0–1)
Bone marrow lesions, 0–9 scale§	77 (47.2)	0 (0–1)
Subchondral bone defects, 0–9 scale	87 (52.7)	1 (0–1)
Cartilage space loss, 0–3 scale	68 (41.2)	0 (0–1)
Osteophytes, 0–9 scale	86 (52.1)	1 (0–1)

* ACR = American College of Rheumatology; AUSCAN = Australian/Canadian Osteoarthritis Hand Index; CMC1 = first carpometacarpal joint; IQR = interquartile range; MR = magnetic resonance; NSAIDs = nonsteroidal antiinflammatory drugs; OA = osteoarthritis; OARSI = Osteoarthritis Research Society International; STT = scaphotrapeziotrapezoid; VAS = visual analog scale.
† Weight or height was not recorded for 5 patients.
‡ One baseline radiograph was missing.
§ Two baseline scores were missing due to unreadable MR images.

Pain and imaging features at two-year follow-up. Frequencies and dimensions of changes in pain and imaging features are shown in Table 2. At the two-year follow-up visit, pain on palpation had decreased or resolved in 32 patients (19.4%) and increased or developed in 33 patients (20%). The number of patients using acetaminophen (58.2%), nonsteroidal antiinflammatory drugs (32.1%), or thumb base splints (10.7%) did not differ from baseline (P = 0.109, P = 0.770, and P = 0.167, respectively) (Table 1).

The majority of patients had no change in MRI scores beyond the smallest detectable change. Structural MRI features generally increased, whereas with inflammatory features such as synovitis and BMLs, both increased and decreased scores were observed. Synovitis most often only changed in one joint (n = 44, 81.5%) (Figure 1), and in fewer cases, synovitis in the CMC1 and STT joints both increased (n = 6), decreased (n = 2), or changed in opposite directions (n = 2). Likewise, a change in BMLs in only one joint (n = 44; 64.7%) (Figure 2) was more common than a paired increase (n = 11), decrease (n = 8), or a change of CMC1 and STT joints in opposing directions (n = 5). Changes in MRI inflammation (synovitis or BMLs) were seen equally often in CMC1 and STT joints (41.4% and 43.1%, respectively). Compared to MRI, radiography less frequently showed an increase in osteophyte scores (6.1% versus 24.2% in thumb bases), JSN scores (13% versus 19.4% in thumb bases), and erosion/cyst scores (3.7% versus 16.4% in CMC1 joints).

Associations between baseline imaging features and change in pain on palpation. Baseline synovitis and BML scores were not associated with an increase in pain after two years (OR 1.13 [95% CI 0.83–1.53] and OR 1.11 [95% CI 0.96–1.27], respectively). Similarly, baseline scores of these features were not associated with a decrease in pain after two years (OR 0.84 [95% CI 0.60–1.19] for synovitis and OR 0.95 [95% CI 0.80–1.12] for BMLs). Baseline radiographic osteophyte scores were not associated with change in pain on palpation after two years after adjustment and stratification for change in MRI features (Tables 3 and 4).

Associations between change in imaging features and change in pain on palpation. An increase in synovitis or BMLs was associated with increased pain after adjustment for the presence of baseline radiographic osteophytes (Table 3). Increases in radiographic osteophytes or JSN were not associated with increased pain (OR 0.95 [95% CI 0.19−4.7] and OR 0.87 [95% CI 0.27−2.81], respectively). Likewise, a decrease in BMLs seemed to be associated with a decrease in pain, although CIs included no effect (Table 3). Decreases in synovitis in patients with baseline pain were rare (n = 7), therefore associations were not computed. In sensitivity analyses, with radiographic JSN to reflect structural damage, effect estimates of the associations of change in MRI features with course of pain did not change (Supplementary Table 1, available on *the Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract).

Table 2. Two-year changes in pain and MR features of the right thumb base in 165 patients with hand osteoarthritis*

		Decrease				Stable				Increase			
	SDC	No.	Min.	Median	Max.	No.	Min.	Median	Max.	No.	Min.	Median	Max.
Pain													
Thumb base													
Self-reported pain	–	26	–	–	–	121	–	–	–	18	–	–	–
Self-reported pain/stiffness	–	23	–	–	–	124	–	–	–	18	–	–	–
Pain on palpation	–	32	−3	−1	−1	100	NA	0	NA	33	1	1	2
MR features													
CMC1													
Synovitis†	0.40	11	−1.00	−0.50	−0.50	134	−0.25	0	0.25	18	0.50	0.63	1.00
Bone marrow lesions‡	0.93	17	−2.50	−1.25	−1.00	115	−0.75	0	0.75	30	1.00	1.38	4.50
Subchondral bone defects	0.60	0	NA	NA	NA	130	−0.50	0	0.50	35	0.75	1.00	2.25
Cartilage space loss	0.35	6	−0.50	−0.50	−0.50	139	0	0	0	20	0.50	0.50	1.50
Osteophytes	0.46	1	NA	−0.50	NA	138	0	0	0	26	0.50	0.50	1.00
Subluxation	0.24	0	–	–	–	159	–	–	–	6	–	–	–
STT joint													
Synovitis§	0.39	15	−3.00	−0.50	−0.50	124	−0.25	0	0.25	21	0.50	1.00	1.00
Bone marrow lesions†	0.79	23	−3.00	−1.50	−1.00	117	−0.75	0	0.75	23	1.00	1.50	3.50
Subchondral bone defects	0.53	4	−1.25	−1.00	−0.75	134	−0.50	0	0.50	27	0.75	1.00	2.25
Cartilage space loss	0.37	6	−2.50	−1.00	−0.50	137	0	0	0	22	0.50	0.50	1.50
Osteophytes	0.31	1	NA	-0.50	NA	147	0	0	0	17	0.50	0.50	1.00
CMC1 and/or STT joints													
Synovitis§	–	22	−3.00	−0.50	−0.50	108	−0.50	0	0.25	30	0.25	1.00	2.00
Bone marrow lesions‡	–	27	−5.50	−2.00	−0.25	99	−1.50	0	1.25	36	0.50	1.63	7.50
Subchondral bone defects	–	4	−1.25	−1.00	−0.75	109	−0.75	0	0.75	52	0.25	1.25	3.50
Cartilage space loss	–	10	−2.50	−0.50	−0.50	123	0	0	0.50	32	0.50	0.50	2.00
Osteophytes	–	2	−0.50	−0.50	−0.50	123	0	0	0	40	0.50	0.50	1.50

* CMC1 = first carpometacarpal joint; Max. = maximum; Min. = minimum; MR = magnetic resonance; NA = not applicable; SDC = smallest detectable change; STT = scaphotrapeziotrapezoid.
† Two change scores were missing due to unreadable MR images.
‡ Three change scores were missing due to unreadable MR images.
§ Five change scores were missing due to unreadable MR images.

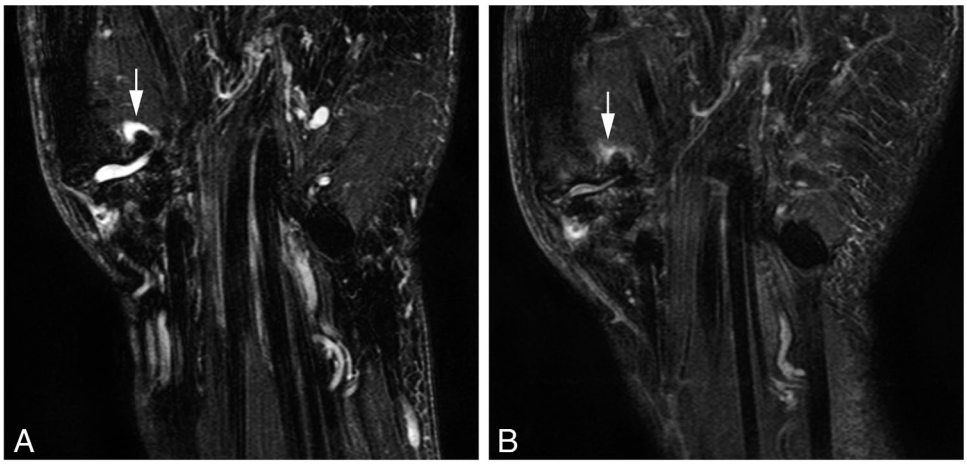

Figure 1. Coronal fat saturated T2-weighted fast spin-echo magnetic resonance imaging from a study participant showing an increase in synovitis in the first carpometacarpal joint (**arrows**) at a two-year follow-up visit (**A**) compared to baseline (**B**).

Interaction between osteophytes and change in inflammatory MRI features. To explore whether the association between an increase in inflammatory MRI features and an increase in pain on palpation was different in thumb bases with radiographic damage at baseline, we stratified these analyses for the presence of radiographic osteophytes at baseline. Due to low numbers, synovitis and BMLs were assessed together in these analyses. As shown in Table 4, in joints without baseline osteophytes, an increase in inflammatory MRI features (synovitis or BMLs) was associated with increased pain (OR 4.3 [95% CI 1.25–14.8]). However, when osteophytes were present at baseline, the association between an increase in MRI inflammation and increased pain was stronger than expected from the combination of separate effects (OR 11.0 [95% CI 3.35–36.1]). The proportion of this association attributable to interaction is as follows: (11.0–1–3.3–0.24)/11.0 = 59% (95% CI 12–100%). Sensitivity analyses in which we stratified for the presence of JSN at baseline instead of osteophytes, and in which we additionally adjusted for JSN scores at baseline, revealed similar results (Supplementary Tables 2 and 3, available on *the Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24355/abstract).

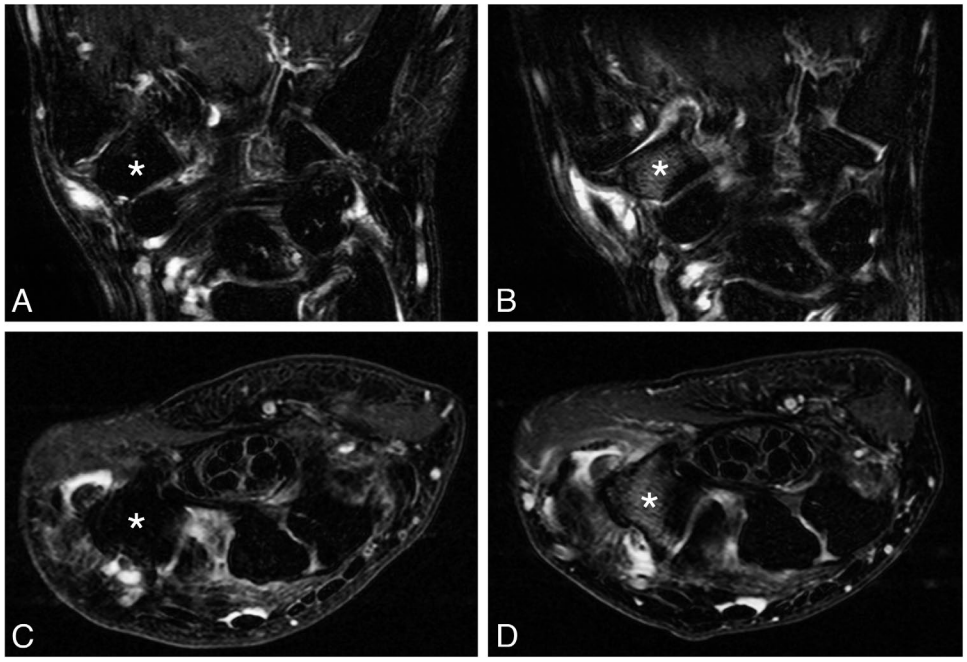

Figure 2. Coronal (**A** and **B**) and axial (**C** and **D**) fat saturated T2-weighted fast spin-echo magnetic resonance imaging from a study participant showing decrease in bone marrow lesions in the trapezium bone (**asterisks**) at a two-year follow-up visit (**A** and **C**) compared to baseline (**B** and **D**).

Table 3. Longitudinal associations between change in MRI-defined synovitis or BMLs and change in thumb base pain on palpation in 165 patients with hand osteoarthritis after 2-year follow-up*

	Outcome			
	Yes	No	Crude OR (95% CI)	Adjusted OR (95% CI)†
Associations with increased pain on palpation (in joints without maximum pain; n = 154)				
Delta synovitis‡				
Stable/decrease	20	101	1	1
Increase	12	16	3.70 (1.49–9.2)	3.44 (1.28–9.3)
Delta bone marrow lesions§				
Stable/decrease	16	102	1	1
Increase	15	18	5.1 (2.15–12.1)	5.1 (2.10–12.6)
Baseline radiographic osteophytes¶				
Absent	13	73	1	1
Present	20	47	2.11 (0.94–4.7)	1.73 (0.73–4.1)
Associations with decreased pain on palpation (in joints without maximum pain; n = 65)				
Delta synovitis#				
Stable/increase	18	19	–	–
Decrease	4	3	–	–
Delta bone marrow lesions**				
Stable/increase	11	17	1	1
Decrease	12	7	2.65 (0.80–8.8)	2.67 (0.80–8.9)
Baseline radiographic osteophytes				
Absent	11	9	1	1
Present	21	24	0.72 (0.25–2.06)	0.78 (0.26–2.28)

* 95% CI = 95% confidence interval; BMLs = bone marrow lesions; MRI = magnetic resonance imaging; OR = odds ratio.
† Adjustments were made for the other imaging scores of features in this table.
‡ Five missing change scores due to unreadable MR images.
§ Three missing change scores due to unreadable MR images.
¶ One missing baseline radiograph.
# Five missing change scores due to unreadable MR images. Synovitis had to be present at baseline to study decrease, resulting in n < 65.
** Three missing change scores due to unreadable MR images. BMLs had to be present at baseline to study decrease, resulting in n < 65.

DISCUSSION

In this study, we describe the two-year natural course of pain and osteoarthritic MRI features in the thumb base and their associations in patients with hand OA. While thumb base pain levels fluctuated over time, MRI features and radiographic damage remained stable in the majority of patients. In those individuals in whom MRI features did change, structural features such as SBDs, cartilage space loss, and osteophytes generally deteriorated, whereas in inflammatory features, including synovitis and BMLs, changes in either direction were seen. MRI features in the CMC1 and the STT joints had a comparable course over two-year follow-up.

Baseline MRI inflammation was not associated with change in pain on palpation. However, an increase in synovitis or BMLs was strongly associated with increased pain, also after adjustment for

Table 4. Number of thumb base joints with increased pain on palpation (yes/no) and associations of increased MR inflammatory features (synovitis or BMLs) with increased pain, stratified for baseline radiographic osteophytes, in 154 patients without maximum thumb base pain at baseline*

	Delta inflammatory MR features			
	Stable/decrease	OR (95% CI)	Increase	OR (95% CI)
Baseline osteophytes				
Absent	5/51†	1	8/19†	4.3 (1.25–14.8)
Present	4/33†	1.24 (0.31–4.9)	14/13†	11.0 (3.35–36.1)

* Seven patients were excluded due to missing data on at least one imaging feature. BMLs = bone marrow lesions; MR = magnetic resonance.
† Number of joints in the thumb base with increased pain on palpation, with the left number indicating the number of patients with increased pain and the right number indicating patients with no increased pain.

radiographic damage. Likewise, a decrease in BMLs appeared to be associated with decreased pain, although less markedly. The number of thumb bases with a decrease in synovitis was too small to estimate associations with a decrease in pain. All associations between imaging features and pain were on a thumb base level since pain on palpation was inevitably examined for the thumb base as a whole due to the close proximity of CMC1 joints and STT joints to each other.

Few studies have investigated the longitudinal relationship between inflammatory MRI features and pain in hand OA. Previous studies have shown that in interphalangeal OA, an increase in synovitis was associated with more pain, less synovitis was associated with less pain, and also that fluctuation in BMLs amplified this effect of synovitis on change in pain (9,10). These studies also suggest that BMLs mainly have an additive effect when accompanying synovitis, and that synovitis is the main driver of pain (6,10). Our study shows that a longitudinal association between inflammatory MRI features and pain on palpation is also present in thumb base OA. However, in our study, associations with BMLs appeared somewhat stronger than with synovitis, which may suggest that in thumb base OA, BMLs do not merely amplify the effect of synovitis. However, the small number of patients in whom changes in synovitis and BMLs occurred in this study precluded formal assessment of interaction between synovitis and BMLs. Further study is warranted to investigate whether associations between synovitis, BMLs, and pain are different in the thumb base compared to the interphalangeal joints.

In a previous cross-sectional analysis of this hand OA cohort (8), we showed that radiographic damage was a more important determinant of pain in the thumb base than synovitis or BMLs were, which contrasts findings of studies in interphalangeal OA (6,7). The same study demonstrated that the combined presence of inflammation and structural damage in the thumb base had an additive effect on pain. We now show that a change in synovitis and BMLs was associated with a change in pain, even after adjustment for radiographic damage. Subsequently, stratified analyses revealed that this association was strongest in joints where radiographic damage was present at baseline. Taking the results of these two studies together, radiographic damage seems to be the most important feature associated with pain in thumb base OA cross-sectionally, though a change in inflammatory features could still have a relevant effect on the course of pain.

The role of inflammation in the pathogenesis of osteoarthritic joint pain was already discussed in an excellent seminar published over a decade ago (23). Recently, a review by different authors corroborated the proposed mechanisms, though definite proof is yet to be found (24). Peripheral nociceptive pain could arise from ongoing tissue injury or inflammation of innervated tissues, such as the subchondral bone, periosteum, and synovium. The cartilage itself is aneural but can still be involved by releasing cytokines and other signaling molecules that can sensitize pain pathways at the peripheral, spinal, or cortical compartment. Pain sensitization might explain why associations between decreased MRI features and decreased pain are smaller compared to increased MRI features and increased pain, as pathways can still remain sensitized after the inflammation subsides (23,24).

The relatively low number of thumb base joints with radiographic progression after two-year follow-up is in line with results from a previous study in 172 patients with hand OA, of whom only 8 (4.7%) had osteophyte progression and even less (n = 5, 2.9%) had JSN progression in the CMC1 joints after two years (25). After 6-year follow-up, only a small proportion of CMC1 and STT joints showed radiographic osteophyte progression (16.5% and 1.5%) or JSN progression (10.5% and 6.2%) (26). Although radiographic progression did not appear to affect pain levels in this study, the low number of joints showing radiographic progression prevents the ability to form strong conclusions about these findings, and a longer follow-up period may be needed to investigate this relationship.

In our study, increase in structural damage was more often seen on MRI than on radiography. The higher sensitivity of MRI to detect structural damage was also shown in a recent cross-sectional study (27). Currently, structural damage assessed on radiographs is considered the gold standard. Whether an increase in structural damage on MRI that is not visible on radiography is clinically relevant should be investigated in future studies.

To our knowledge, this is the first study describing the course of clinical and MRI parameters in thumb base OA in a study with a considerable sample size. This cohort, recruited from a rheumatology outpatient clinic in a secondary and tertiary referral center, is a good representation of hand OA patients who are in need of and could benefit from treatment but who may be different from a primary care population; hence, results should be extrapolated with caution. As a result of including patients with hand OA, but not necessarily thumb base OA, our cohort consisted of patients with a wide variety of thumb base OA disease stages.

An important limitation of this study is the low number of patients in whom a change in pain, MRI features, or structural damage occurred, which demonstrates that the natural course of thumb base OA is a slow process. As a consequence, the estimated associations are less accurate, which is reflected by wide CIs, especially for the stratified analyses. Future studies investigating the longitudinal relationship between pain, MR-defined inflammation, and radiographic damage with a large group size and longer follow-up are therefore warranted. Additionally, analyses in the setting of a positive clinical trial would provide more insight in associations with improvement in pain. Another limitation might be the possible use of over-the-counter analgesics and thumb base splints in this observational cohort. However, in general, the efficacy of analgesics for treating OA pain is small (28,29), and even though a recent meta-analysis showed positive effects of thumb base splinting on pain (30), there is no evidence that these interventions influence MRI features. Therefore, we believe these interventions might only have introduced

nondifferential misclassification, but not bias, in the studied associations. Last, pain experience can be modulated by psychosocial and other contextual factors (23,24), which were not taken into account. Although, by using pain on palpation—instead of self-reported pain—these effects were mitigated, and more importantly, there is no reason to believe that these contextual factors can influence MRI features.

In addition to providing more insight in the course and prognosis of thumb base OA, this study suggests inflammation in the thumb base could be explored as a potential treatment target. This may appear to contrast negative findings from clinical trials of intraarticular glucocorticoid injections in the thumb base (31), though the lack of trials with positive outcomes could also be related to the inclusion of patients without inflammation. Therefore, trials selecting patients based on the presence of thumb base inflammation, and not primarily radiographic damage as has been done before, may generate different results. Indeed, a recently published trial of prednisolone in interphalangeal OA that only included patients with objectifiable inflammation of at least one interphalangeal joint showed significant and clinically meaningful results (32), whereas previous trials of glucocorticoids in hand OA without confirmed inflammation at baseline were inconclusive (33).

In conclusion, over the course of 2 years, thumb base pain fluctuated. Osteoarthritic features on MRI of the thumb base changed in a minority of patients with hand OA, in whom structural features mostly deteriorated and in whom inflammatory features changed in either direction. Changes in synovitis and BMLs were associated with changes in pain, mainly in patients with radiographic damage. Therefore, while radiographic damage may be the main determinant of pain in thumb base OA, the present study shows that a change in inflammatory features in the thumb base may still have a relevant effect on pain.

ACKNOWLEDGMENTS

We thank the patients of the HOSTAS cohort for participation in this study, research physicians W. Damman and R. Liu, research nurses B. A. M. J. van Schie-Geyer and S. Wongsodihardjo, and data managers J. W. M. van Krol-Berkel and C. H. Kromme in the rheumatology department, and technicians in the radiology department of the Leiden University Medical Center for support in data collection.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. van Beest and Kloppenburg had full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. van Beest, Kloppenburg, Kroon.
Acquisition of data. van Beest, Kroon, Reijnierse, Kloppenburg, Kroon.
Analysis and/or interpretation of data. van Beest, Rosendaal, Kloppenburg, Kroon.

REFERENCES

1. Goislard de Monsabert B, Vigouroux L, Bendahan D, Berton E. Quantification of finger joint loadings using musculoskeletal modelling clarifies mechanical risk factors of hand osteoarthritis. Med Eng Phys 2014;36:177–84.
2. Li ZM, Tang J. Coordination of thumb joints during opposition. J Biomech 2007;40:502–10.
3. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: a hand osteoarthritis subset requiring a distinct approach. Best Pract Res Clin Rheumatol 2017;31:649–60.
4. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis 2009;68:8–17.
5. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601–10.
6. Liu R, Damman W, Reijnierse M, Bloem JL, Rosendaal FR, Kloppenburg M. Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis. Osteoarthritis Cartilage 2017;25:1093–99.
7. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, Sesseng S, van der Heijde D, Kvien TK. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. Ann Rheum Dis 2012;71:899–904.
8. Kroon FP, van Beest S, Ermurat S, Kortekaas MC, Bloem JL, Reijnierse M, et al. In thumb base osteoarthritis structural damage is more strongly associated with pain than synovitis. Osteoarthritis Cartilage 2018;26:1196–202.
9. Haugen IK, Christensen BS, Boyesen P, Sesseng S, van der Heijde D, Kvien TK. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. Ann Rheum Dis 2016;75:702–8.
10. Van Beest S, Damman W, Liu R, Reijnierse M, Rosendaal FR, Kloppenburg M. In finger osteoarthritis, change in synovitis is associated with change in pain on a joint-level; a longitudinal magnetic resonance imaging study. Osteoarthritis Cartilage 2019;27:1048–56.
11. Damman W, Liu R, Kroon FP, Reijnierse M, Huizinga TW, Rosendaal FR, et al. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand Osteoarthritis in Secondary Care Cohort. J Rheumatol 2017;44:1659–66.
12. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage 2002;10:863–9.
13. Bijsterbosch J, Wassenaar MJ, le Cessie S, Slagboom PE, Rosendaal FR, Huizinga TW, et al. Doyle Index is a valuable additional pain measure in osteoarthritis. Osteoarthritis Cartilage 2010;18:1046–50.
14. Kroon FP, Conaghan PG, Foltz V, Gandjbakhch F, Peterfy C, Eshed I, et al. Development and reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging scoring system. J Rheumatol 2017;44:1694–8.
15. Kroon FP, Peterfy CG, Conaghan PG, Foltz V, Gandjbakhch F, Eshed I, et al. Atlas for the OMERACT Thumb Base Osteoarthritis MRI Scoring System (TOMS). RMD Open 2018;4:e000583.
16. Kroon FP, van Beest S, Gandjbakhch F, Peterfy CG, Chen S, Conaghan PG, et al. Longitudinal reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System (TOMS). J Rheumatol 2019;46:9.
17. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. J Clin Epidemiol 1993;46:423–9.
18. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:A1–56.

19. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis 2005;64:179–82.
20. Rothman KJ. Epidemiology: an introduction. Second edition. Oxford, New York: Oxford University Press; 2012.
21. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology 1992;3:452–6.
22. Micallef L, Rodgers P. eulerAPE: drawing area-proportional 3-Venn diagrams using ellipses. PLoS One 2014;9:e101717.
23. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005;365:965–73.
24. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393: 1745–59.
25. Botha-Scheepers S, Riyazi N, Watt I, Rosendaal FR, Slagboom E, Bellamy N, et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. Ann Rheum Dis 2009;68:1260–4.
26. Bijsterbosch J, Meulenbelt I, Watt I, Rosendaal FR, Huizinga TW, Kloppenburg M. Clustering of hand osteoarthritis progression and its relationship to progression of osteoarthritis at the knee. Ann Rheum Dis 2014;73:567–72.
27. Van Beest S, Kroon FP, Kroon HM, Damman W, Liu R, Bloem JL, et al. Assessment of osteoarthritic features in the thumb base with the newly developed OMERACT magnetic resonance imaging scoring system is a valid addition to standard radiography. Osteoarthritis Cartilage 2019;27:468–75.
28. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015;162:46–54.
29. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2017;390:e21–33.
30. Buhler M, Chapple CM, Stebbings S, Sangelaji B, Baxter GD. Effectiveness of splinting for pain and function in people with thumb carpometacarpal osteoarthritis: a systematic review with meta-analysis. Osteoarthritis Cartilage 2019;27:547–59.
31. Kroon FP, Rubio R, Schoones JW, Kloppenburg M. Intra-articular therapies in the treatment of hand osteoarthritis: a systematic literature review. Drugs Aging 2016;33:119–33.
32. Kroon FP, Kortekaas MC, Boonen A, Böhringer S, Reijnierse M, Rosendaal FR, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. Lancet 2019;394:1993–2001.
33. Kroon FP, Carmona L, Schoones JW, Kloppenburg M. Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. RMD Open 2018;4:e000734.