Inflammation as a target for treatment in hand osteoarthritis

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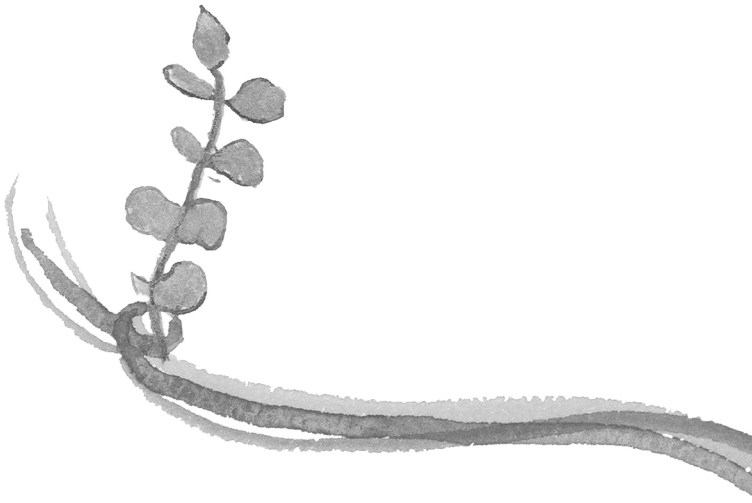
CHAPTER 8

Two-year changes in MRI-features and pain in thumb base osteoarthritis



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ABSTRACT

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

Methods. Patients of the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort who underwent hand radiography, MRI and clinical examination of the right thumb base at baseline and two-year follow-up were studied. Pain on palpation of the thumb base (0-3) was assessed. MRI were scored with the OMERACT thumb base osteoarthritis MRI scoring-system (TOMS) for synovitis, bone marrow lesions (BMLs), subchondral bone defects (SBDs), cartilage space loss, osteophytes, and subluxation. Radiographs were assessed for osteophytes and joint space narrowing. We studied associations of changes in synovitis and BMLs with changes in pain with logistic regression, adjusted for radiographic damage.

Results. Of 165 patients (83.0% women, mean 60.7 years) 65 had thumb base pain at baseline. At two-year follow-up, pain had decreased in 32 and increased in 33 patients. MRI-features remained stable in most patients. Structural MRI-features generally deteriorated, while synovitis and BMLs improved in some and deteriorated in others. Change in radiographic osteophytes rarely (n=10) occurred. Increased synovitis (OR 3.4 (95% CI 1.3-9.3)) and increased BMLs (OR 5.1 (2.1-12.6)) were associated with increased pain. Decreased BMLs were associated with decreased pain (OR 2.7 (0.8-8.9)), but synovitis decrease occurred too infrequently to calculate associations.

Conclusion. Over two years, thumb base pain fluctuated, while MRI-features changed in a minority of hand osteoarthritis patients. Changes in synovitis and BMLs were associated with changes in pain, 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 which includes the first carpometacarpal (CMC-1) 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 focussed on the hand as a whole or the interphalangeal joints specifically, and American College of Rheumatology (ACR) classification criteria do not distinguish between interphalangeal and thumb base OA. Therefore, our knowledge on this hand OA subset and its natural course is limited.

Alongside structural joint damage – 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.[5-7] 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.[5,6] Yet, in a study investigating these aspects in thumb base OA, the opposite was seen: while synovitis and BMLs were associated with pain, structural damage was found to be its most important determinant.[7]

Longitudinal imaging studies of interphalangeal OA have shown that a change in MRI inflammation was associated with a change in pain levels.[8,9] 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 and MRI-features in thumb base OA, and their association.

METHODS

Study design

We used longitudinal data of 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 recruitment and selection have been published elsewhere.[10]

Participants with baseline and two-year follow-up data available were included in this analysis (supplementary figure S1). Written informed consent was obtained from all participants. The study was approved by the Leiden University Medical Center medical ethics committee.

Demographics and clinical assessment

Demographics and clinical characteristics were collected by standardized questionnaires, including self-reported thumb base pain and stiffness during the last month (absent/present), the Australian/Canadian hand OA index (AUSCAN),[11] self-reported hand pain on

a visual analogue scale (VAS, range 0-100 millimeter). Trained research nurses examined the thumb bases for pain upon palpation on a semi-quantitative scale (0-3),[12] and bony swelling (absent/present).

MRI acquisition and scoring

MR images of the right CMC-1 and STT joints were obtained at baseline and two-year follow-up visits using an MSK-Extreme 1.5 T extremity MR imaging scanner (GE, Wisconsin, USA). The following sequences were acquired: coronal T1-weighted (T1-w) fast spin echo (FSE) images (repetition time [TR]/echo time [TE] 575/≤11 ms), axial T1-w FSE images (TR/TE 575/≤10.5 ms), coronal T2-w FSE images with frequency selective fat saturation (fat sat) (TR/TE 3000/61.8 ms), and axial T2-w FSE fat sat images (TR/TE 3000/60 ms). 18 coronal slices (slice thickness 2 mm, slice gap 0.2 mm) and 20 axial slices (slice thickness 3 mm, slice gap 0.3 mm) were obtained. No intravenous contrast was administered.

Images were scored pairwise in chronological order by two readers (SvB; FPBK), who scored independently while blinded for clinical and radiography data, using TOMS.[13-15] Synovitis, BMLs, subchondral bone defects (SBDs), cartilage space loss and osteophytes were scored 0-3 for the CMC-1 and STT joints, and CMC-1 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 (CMC-1) and 9 (STT). For changes in synovitis, SBDs and BMLs half-point increments were used to indicate within-grade changes. Interrater reliability was moderate/good for all baseline features (mixed model, exact agreement, average measure, ICCs 0.59-0.92, CMC-1 subluxation prevalence-adjusted bias-adjusted kappa [PABAK] 0.77) and change scores (mixed model, exact agreement, average measure, ICCs 0.53-0.81, CMC-1 subluxation PABAK 0.88).[16]

Radiograph acquisition and scoring

Postero-anterior hand radiographs were obtained at baseline and two-year follow-up. Images were scored paired in chronological order by two readers (SvB; HMK), who scored in consensus while blinded for clinical and MRI data. Osteophytes and joint space narrowing (JSN) in CMC-1 (0-3) and STT (absent/present) joints, and erosions and cysts in CMC-1 joint (absent/present) were scored according to the OARSI atlas.[17] Intraobserver reliability based on a subset of 20 randomly selected patients was excellent (prevalence-adjusted bias-adjusted kappa [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 taken as the starting point for the current study.[7] To ascertain that those findings also applied to the present study, which concerns a selection of the study population with follow-up data available (supplementary figure S1) in which different readers scored the radiographs, we first repeated the cross-sectional analyses of associations between baseline synovitis, BMLs and radiographic osteophytes (determinants) and presence of pain on palpation (outcome).

Next, we determined the smallest detectable change (SDC) for use as a threshold for increase and decrease in MRI-scores.[18] Since pain was assessed for the thumb base as a whole, change scores of CMC-1 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 one joint increased while the other decreased. Radiographic baseline scores of CMC-1 and STT joints were combined and dichotomized similarly: absent in CMC-1 and STT versus present in CMC-1 or STT.

Using logistic regression, 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 (CI).

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, figure 1) or decrease in pain on palpation (excluding thumb bases without pain at baseline, supplementary figure S2) over two years.

Second, we assessed whether a two-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 S2). Thumb bases with stable or decreased imaging features served as the reference category.

Third, we examined the reverse situation for the MRI-features, excluding thumb bases without synovitis or BMLs and without pain at baseline (supplementary figure S2). Thumb bases with stable or increased MRI-features served as the reference category.

All analyses were done in univariable and multivariable models, adjusting for the 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 dataset.

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 presence or absence of baseline radiographic osteophytes. The attributable proportion was estimated, which reflects the proportion of the odds ratio for the doubly exposed group attributable to interaction.[19,20]

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 by JSN scores, and (2) added JSN scores as an additional covariate to the models.

Data were analysed using SPSS for Windows, version 23.0 (IBM SPSS statistics, New York, USA). Area Proportional Euler diagrams were drawn using eulerAPE, version 3.0.0 (freely available at http://www.eulerdiagrams.org/eulerAPE/).[21]

RESULTS

Study population

In the HOSTAS cohort, 202 patients underwent MRI of the right thumb base at baseline, of whom 166 also did at two-year follow-up (supplementary figure S1). One patient was excluded due to prior joint anatomy-altering thumb base surgery. The majority of the included 165 patients fulfilled the ACR criteria, were middle-aged and female (table 1). Baseline characteristics (including imaging scores) of patients included in the analyses were not different from those who only underwent baseline MRI.

Pain and imaging features at baseline

At baseline, 93 (56.4%) of the patients indicated to frequently have had pain in the right thumb base in the previous month, and 65 (39.4%) had 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 (CMC-1 or STT) with synovitis or BMLs (table 1). All MRI-features were more prevalent in the CMC-1 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 CMC-1 joints and 52% of STT joints). Radiographic osteophytes were present in 74 thumb bases (45%), primarily in the CMC-1 joints.

As expected, we reaffirmed previous findings 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 (synovitis: 3.05 [1.35–6.9], BMLs: 2.50 [1.28–4.9]) attenuated after adjustment for osteophytes (synovitis: 1.63 [0.66–4.0], BMLs: 1.10 [0.49–2.46]).[7]

Pain and imaging features at two-year follow-up

Frequencies and dimensions of changes in pain and imaging features are presented 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 majority of patients had no change in MRI scores beyond the smallest detectable change. Structural MRI-features generally increased, while in 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 the CMC-1 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 CMC-1 and STT changing in opposing directions (n=5). Change in MRI inflammation (synovitis or BMLs) was seen equally often in the CMC-1 and STT joints (41.4% versus 43.1%).

Table 1. Baseline characteristics of n=165 patients with hand osteoarthritis (OA).

			Baseline	
Demographics				
Sex, n (%) female			137	(83.0)
Age, years			60.7	(8.3)
Fulfilling ACR criteria for hand OA, n (%)			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, n (%)			93	(56.4)
Self-reported stiffness of right thumb base, n (%)			58	(35.2)
Pain on palpation of right thumb base present, n (%)			65	(39.4)
Bony swelling of right thumb base, n (%)			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, n (%)			85	(51.5)
Self-reported use of NSAIDs, n (%)			50	(30.3)
Self-reported use of thumb base splint, n (%)			11	(6.7)
Radiography† (right hand)				
CMC-1				
OARSI osteophyte present, n (%)			74	(45.1)
OARSI joint space narrowing present, n (%)			61	(37.2)
STT				
OARSI osteophyte present, n (%)			9	(5.5)
OARSI joint space narrowing present, n (%)			32	(19.5)
MR Imaging (right hand)	**present, n**	**(%)**	**median**	**(IQR)**
CMC-1				
Synovitis‡, (0–3 scale)	69	(42.3)	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)
Subluxation, (absent/present)	30	(18.2)		
STT				
Synovitis‡, (0–3 scale)	65	(39.9)	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)

Mean (SD) or median (IQR) unless stated otherwise. AUSCAN, Australian/Canadian osteoarthritis hand index; CMC-1, first carpometacarpal joint; MR, magnetic resonance; NSAIDs, non-steroidal anti-inflammatory drugs; STT, scaphotrapeziotrapezoid joint. *Weight or height was not recorded for five patients, †one baseline radiograph was missing, and ‡two baseline scores were missing due to unreadable MR images.

Compared with MRI, radiography less frequently showed an increase in osteophyte scores (6.1% versus 24.2% of thumb bases), JSN scores (13% versus 19.4% of thumb bases) and erosion/cyst scores (3.7% versus 16.4% of CMC-1 joints).

Associations between baseline imaging features and change in pain

Baseline synovitis and BML scores were not associated with an increase in pain after two years (ORs 1.13 [0.83–1.53] and 1.11 [0.96–1.27], respectively). Similarly, baseline scores of these features were not associated with a decrease in pain after two years (synovitis: 0.84 [0.60–1.19], BMLs: 0.95 [0.80–1.12]). Baseline radiographic osteophyte scores were not associated with change in pain after two years, when adjusted or stratified for change in MRI-features (table 3 and 4).

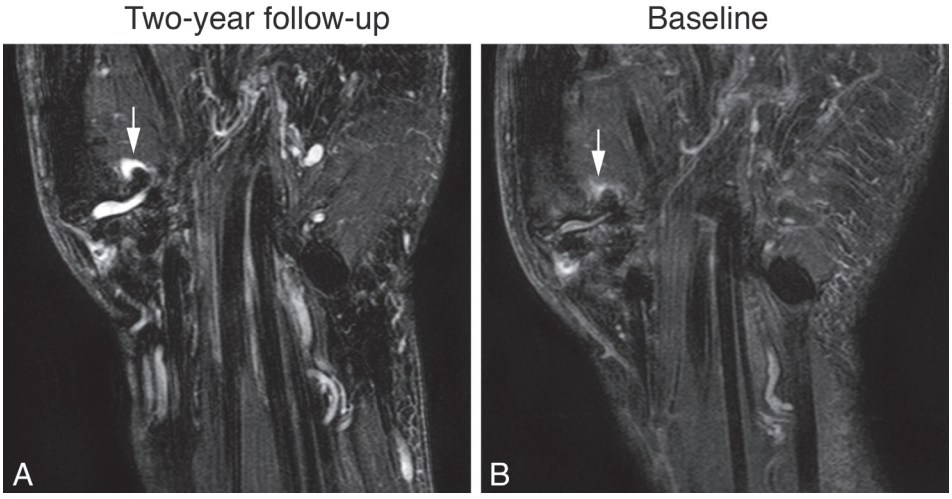

Figure 1. Coronal fat saturated T2-weighted FSE MR imaging showing increase in synovitis in the CMC-1 joint (*arrows*) at the two-year follow-up visit (A) compared to baseline (B).

Associations between change in inflammatory MR features and change in pain

An increase in synovitis or BMLs was associated with increased pain, also after adjustment for the presence of baseline radiographic osteophytes (table 3). Increases in radiographic osteophytes or JSN were not associated with increased pain (ORs 0.95 [0.19–4.7] and 0.87 [0.27–2.81], respectively).

Likewise, a decrease in BMLs seemed to be associated with a decrease in pain, although confidence intervals included no effect (table 3). Decrease of synovitis in patients with baseline pain was 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 S1).

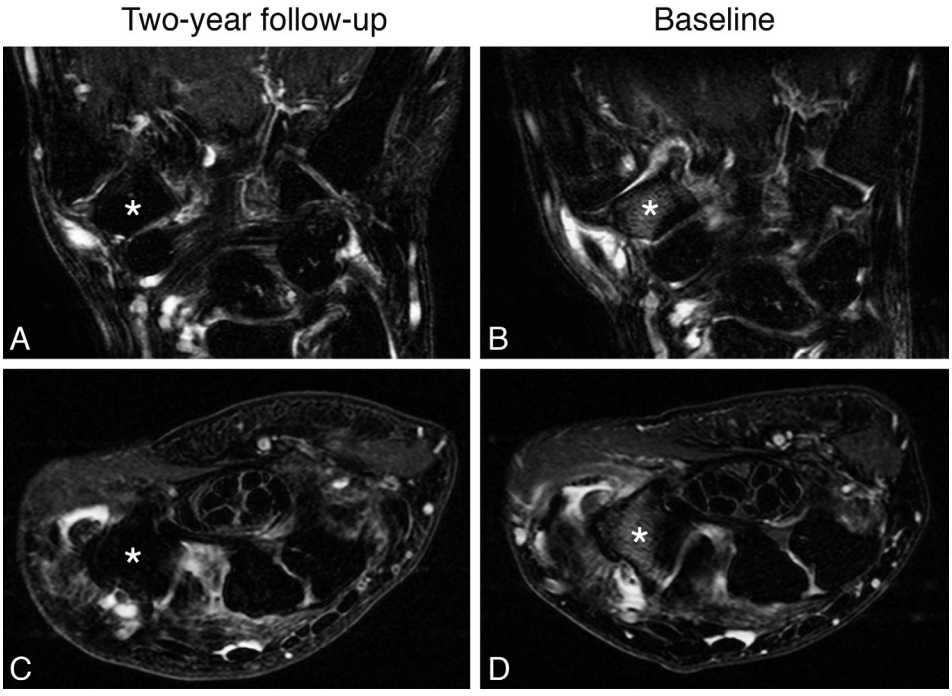

Figure 2. Coronal (A, B) and axial (C, D) fat saturated T2-weighted FSE MR imaging showing decrease in bone marrow lesions in the trapezium bone (*asterisks*) at the two-year follow-up visit (A, C) compared to baseline (B, D).

Interaction between osteophytes and change in inflammatory MR features

To explore whether the association between an increase in inflammatory MRI-features and an increase in pain 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 [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 [3.35–36.1]). The proportion of this association attributable to interaction is (11.0–1–3.3–0.24)/11.0 = 59% [95% CI 12%–100%]. Sensitivity analyses in which we stratified for the presence of baseline JSN instead of osteophytes, and in which we additionally adjusted for baseline JSN scores revealed similar results (supplementary tables S2 and S3).

Table 2. Two-year changes in pain and MR features of the right thumb base in n=165 patients

		Decrease			Stable				Increase			
		N	Median			N	Median			N	Median		
			min.		max.		min.		max.		min.		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	n/a	0	n/a	33	1	1	2
MR features	**SDC**												
CMC-1													
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	n/a	n/a	n/a	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	n/a	-0.50	n/a	138	0	0	0	26	0.50	0.50	1.00
Subluxation	0.24	0				159				6			
STT													
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	n/a	-0.50	n/a	147	0	0	0	17	0.50	0.50	1.00
CMC-1 and/or STT													
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

Two/ †three/ ‡five change scores were missing due to unreadable MR images. CMC-1, first carpometacarpal joint; MR, magnetic resonance; STT, scaphotrapeziotrapezoid joint.

Table 3. Longitudinal associations between change in MRI-defined synovitis or BMLs and change in thumb base pain in 165 patients with hand OA after two-year follow-up

	Change in pain		Crude	Adjusted*
	yes	/no, n	OR (95% CI)	OR (95% CI)
Associations with increased pain				
(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				
(in joints with baseline 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)

BMLs, bone marrow lesions; CI, confidence interval; OR, odds ratio. *Adjustments were made for the other imaging scores of features in this table. †Five/‡three missing change scores due to unreadable MR images and §one missing baseline radiograph. ‖Synovitis or ¶BMLs had to be present at baseline to study decrease resulting in n<65.

Table 4. Number of thumb base joints with increased pain (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		Increase	
BL 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)

Associations are presented as odds ratios (95% CI). BL, baseline; CI, confidence interval; MR, magnetic resonance. Seven patients were excluded due to missing data on at least one imaging feature.

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 in whom MRI-features did change, structural features, such as SBDs, cartilage space loss and osteophytes, generally deteriorated, while in inflammatory features, including synovitis and BMLs, changes in either direction were seen. MRI-features in the CMC-1 and the STT joints had a comparable course over the two-year follow-up.

Baseline MRI inflammation was not associated with change in pain. However, an increase in synovitis or BMLs was strongly associated with increased pain, also after adjustment for radiographic damage. Likewise, a decrease in BMLs appeared to be associated with decreased pain, although less markedly. The number of joints 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 CMC-1 and STT joints to each other.

Few studies have investigated the longitudinal relation 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, that less synovitis was associated with less pain, and also that fluctuation in BMLs amplified this effect of synovitis on change in pain.[8,9] These studies also suggest that BMLs mainly have an additive effect when accompanying synovitis, and that synovitis is the main driver of pain.[5,9] Our study shows that a longitudinal association between inflammatory MRI-features and pain 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 a change 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 in this hand OA cohort,[7] we showed that radiographic damage was a more important determinant of pain in the thumb base than synovitis or BMLs were, which contrasted findings of studies in interphalangeal OA.[5,6] 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, but a change in inflammatory features may 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 in the Lancet over a decade ago.[22] Recently, a review by different authors in the same journal corroborates the proposed mechanisms, though definite proof is yet to be found.[23] 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 also 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.[22,23]

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 hand OA patients, of whom merely 8 (4.7%) had osteophyte progression and even less (n=5, 2.9%) had JSN progression in the CMC-1 joints after two years.[24] After six-year follow-up, still only a small proportion of CMC-1 and STT joints showed radiographic osteophyte (16.5% and 1.5%) or JSN (10.5% and 6.2%) progression.[25] Although radiographic progression did not appear to affect pain levels in this study, the low number of joints progressing hampers strong conclusions, and a longer follow-up 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.[26] Currently, structural damage assessed on radiographs is considered the gold standard. Whether (an increase in) structural damage on MRI, 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 that are in need of and could benefit from treatment, but might 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 of the longitudinal relation between pain, MR-defined inflammation and radiographic damage with a large group size and longer follow-up are therefore warranted. In addition, 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 usage 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,[27,28] and even though a recent meta-analysis showed positive effects of thumb base splinting on pain,[29]

there is no evidence that these interventions influence MRI-features. Therefore, we believe these interventions might only have introduced additional noise in the studied associations, but did not introduce bias.

Besides 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 seem to contrast negative findings of clinical trials of intra-articular glucocorticoid injections in the thumb base,[30] 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,[31] whereas previous trials of glucocorticoids in hand OA without confirmed inflammation at baseline were inconclusive.[32]

In conclusion, over the course of two years, thumb base pain fluctuated. Osteoarthritic MRI-features in the thumb base changed in a minority of patients with hand OA, in whom structural features mostly deteriorated and 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, this study shows that a change in inflammatory features in the thumb base may still be relevant effect on pain.

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