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In finger osteoarthritis, change in synovitis is associated with change in pain on a joint-level; a longitudinal magnetic resonance imaging study

S. van Beest † * [a], W. Damman † [a], R. Liu †, M. Reijnierse ‡, F.R. Rosendaal §, M. Kloppenburg † §

† Departments of Rheumatology, Leiden University Medical Center (LUMC), Leiden, the Netherlands
‡ Radiology, Leiden University Medical Center (LUMC), Leiden, the Netherlands
§ Clinical Epidemiology, Leiden University Medical Center (LUMC), Leiden, the Netherlands

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SUMMARY

Objective: To investigate determinants of decrease and increase in joint pain in symptomatic finger osteoarthritis (OA) on magnetic resonance (MR) imaging over 2 years.
Design: Eighty-five patients (81.2% women, mean age 59.2 years) with primary hand OA (89.4% fulfilling American College of Rheumatology (ACR) classification criteria) from a rheumatology outpatient clinic received contrast-enhanced MR imaging (1.5T) and physical examination of the right interphalangeal finger joints 2–5 at baseline and at follow-up 2 years later. MR images were scored paired in unknown time order, following the Hand OA MRI scoring system (HOAMRIS). Joint pain upon palpation was assessed by research nurses. Odds ratios (ORs; 95% confidence intervals) were estimated on joint level (n = 680), using generalized estimating equations (GEE) to account for the within patient effects. Additional adjustments were made for change in MR-defined osteophytes, synovitis, and bone marrow lesions (BMLs).
Results: Of 116 painful joints at baseline, at follow-up: 76 had less pain, 21 less synovitis, and 13 less BMLs. A decrease in synovitis (OR = 5.9; 1.12–31.0), but not in BMLs (OR = 0.39; 0.10–1.50), was associated with less pain. Of 678 joints without maximum baseline pain, at follow-up: 115 had increased pain, 132 increased synovitis, 96 increased BMLs, and 44 increased osteophytes. Increased synovitis (OR = 1.81; 1.11–2.94), osteophytes (OR = 2.75; 1.59–4.8), but not BMLs (OR = 1.14; 0.81–1.60), was associated with increased pain. Through stratification it became apparent that BMLs were mainly acting as effect modifier of the synovitis–pain association.
Conclusion: Decrease in MR-defined synovitis is associated with reduced joint pain, identifying synovitis as a possible target for treatment of finger OA.
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Introduction

Finger osteoarthritis (OA), a subset of hand OA that typically affects the proximal and distal interphalangeal joints, is the most prevalent OA phenotype in the aging population[1,2]. OA results in cartilage degradation, but also affects the subchondral bone, and results in bone proliferation with osteophyte formation, accompanied by local synovial inflammation[1]. Hand OA has a high disease burden, where joint pain is a main concern, with patients suffering in a similar degree as in rheumatoid arthritis[3–5]. However, current treatment options to alleviate pain are limited in number, effectiveness, and safety[6–8]. The aetiology of pain in hand OA is not well understood. Many factors contribute to pain or alter its perception, for example: local inflammation (synovitis), subchondral bone activity (assessed as bone marrow lesions [BMLs] on magnetic resonance (MR) images), structural changes (osteophytes, cartilage loss,

* Address correspondence and reprint requests to: S. van Beest, Department of Rheumatology, Leiden University Medical Center, C1-R. PO Box 9600, 2300 RC, Leiden, The Netherlands. Tel: 31-71-5261280; Fax: 31-71-5266752.
E-mail addresses: s.van_beest@lumc.nl (S. van Beest), w.damman@lumc.nl (W. Damman), r.liu@lumc.nl (R. Liu), m.reijnierse@lumc.nl (M. Reijnierse), f.r.rosendaal@lumc.nl (F.R. Rosendaal), g.kloppenburg@lumc.nl (M. Kloppenburg).
[a] Both authors contributed equally to the manuscript.

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erosions), genetic predisposition, behaviour, comorbidities, and various psychosocial factors[9–19]. Whereas some of these cannot be changed, others can be modified and are therefore good candidates for targeted treatment. Local inflammation and subchondral bone activity are potential targets, since treatment options might be available[6,20], and synovitis and BMLs have positive associations with joint pain in cross-sectional imaging studies[9–11]. Longitudinal imaging studies have shown that synovitis and BMLs can vary over time and that increased scores were associated with *de novo* joint pain[21]. However, for synovitis and BMLs to be a relevant treatment target, the opposite situation also has to be true: decreasing scores have to associate with loss, or at least attenuation, of joint pain; this is still unclear. Therefore our aim was to investigate the longitudinal associations for MR-defined synovitis and BMLs with joint pain in patients with primary hand OA over a 2-year period.

Patients and methods

Study population

We used data from the Hand OSTeoArthritis in Secondary care (HOSTAS) study, in which consecutive patients diagnosed by their treating rheumatologist with primary hand OA were included between 2009 and 2015[15]. The present analysis concerns patients who received contrast-enhanced magnetic resonance imaging (MRI), which was only performed in a subset of the HOSTAS cohort included between March 2011 to October 2012, at baseline and at follow-up 2 years later. Exclusion criteria were: any other pathological condition explaining the hand symptoms, secondary OA and routine MR contraindications. Written informed consent was obtained from all participants. The study was approved by the Leiden University Medical Center (LUMC) medical ethics committee.

Clininal examination

Demographics and clinical characteristics were collected by standardized questionnaires, including the Dutch-language version of the Australian/Canadian hand OA index (AUSCAN)[22,23]. Self-reported hand pain was assessed by visual analogue scale (range 0–100 mm). Trained research nurses performed the physical examination, assessing the distal interphalangeal (DIPJs), proximal interphalangeal (PIPJs), interphalangeal (IPJs), metacarpophalangeal (MCPJs) and first carpometacarpal (CMC1Js) joints of both hands (30 per patient) for pain upon palpation on a 0–3 scale. Fulfilment of the American College of Rheumatology (ACR) criteria for clinical hand OA[24] was determined. The patient's height, weight and grip strength were assessed during each visit. Maximum right hand cylinder grip strength, measured with a hydraulic hand dynamometer (Saehan Corporation, Masan, South-Korea), was defined as the best performance of two attempts.

Radiography

Baseline dorsopalmar radiographs of both hands were scored 0–4 following Kellgren–Lawrence (KL) scoring[25], assessing the DIPJs, PIPJs, IPJs, MCPJs and CMC1Js (30 joints per patient). Osteophytes and joint space narrowing (JSN) were scored following the Osteoarthritis Research Society International atlas[26]: DIPJs, PIPJs, and CMC1Js from 0 to 3; IPJs and scaphotrapeziotrapezoid joints (STTJs) 0 (absent) or 1 (present). In addition DIPJs and PIPJs (16 joints per patient) were scored following Verbruggen-Veys (VV) anatomical phase scoring[27]. Erosive disease was defined as having $\geq$1 joint in an erosive or remodelled phase. A single reader (WD) scored all radiographs, blinded for demographic and clinical data, with high intraobserver reliability[15].

MR imaging

MR imaging of the right PIPJs and DIPJs ($n = 8$ joints per patient) was performed at baseline and after 2 years, using a 1.5 T extremity MR imaging scanner (GE, Wisconsin, USA). We acquired T1-weighted turbo spin echo (TSE) (T1w) and T2-weighted TSE fat saturated (T2w) sequences in the coronal and axial plane. After gadolinium-chelate (standard dose 0.1 mmol/kg gadoteric acid, Guerbet, France) injection, T1-weighted TSE with fat saturation (T1w-Gd) was performed in the same planes. Details about the protocol have been published previously[28].

One trained reader (WD) scored MR images paired in unknown time order according to the Hand OA MRI scoring system (HOAMRIS)[29]. The scored MR features (0–3, higher scores reflecting worse condition) were:

- synovitis, defined as thickened synovium with contrast enhancement, scored normal (0) or tertiles of presumed maximum volume. As our main focus was on synovitis, we scored this apart from other features to reduce bias, using axial T1w-Gd images with T1w coronal images serving as localizer;
- BML, defined as a lesion with ill-defined margins within the trabecular bone with high signal intensity on T2w images, scored normal (0) or tertiles of affected bone volume (0.5 and 1.0 cm from the articular surface in either direction for DIPJ and PIPJ, respectively) for distal and proximal part of the joint separately (scores were later combined), on axial and coronal T2w images;
- osteophyte, defined as abnormal bone protuberance at joint margins, scored normal (0) or $\leq$3 small osteophytes (1), >3 small osteophytes or $\geq$1 moderate osteophyte (2), or $\geq$1 large osteophyte (3), on axial and coronal T1w images;
- three remaining features as described in detail elsewhere[29]: cysts, defined as sharply marginated bone lesion without cortical break; erosive damage, defined as subchondral bone loss due to erosions, bone attrition, or bone resorption; and cartilage space loss (CSL), defined as loss of the cartilage space based on the inter-bone distance.

The HOAMRIS allows 0.5 increments and decrements over time for synovitis, BML and erosive damage. When, like in our study, chronological order is unknown, one cannot simply allow scoring in 0.5 steps as this would inflate the scoring to a 7-point scale instead of a 4-point scale. Therefore, we applied the following rule: half scores are allowed in a pair only, if one of the pair is a rounded score, which is not zero. For example; the pairs 0–0.5 and 1.5–2.5 are not possible, but 0.5–1 is possible. After deblinding the time order, change scores (delta-scores) were calculated and subsequently any non-integer baseline score was recoded to the whole score given within that pair.

Intrareader reliability, based on 16 randomly selected patients, was high: baseline intraclass correlation coefficients, adjusted for unique joints clustering within each patient, were 0.91, 0.91 and 0.90, and percentages exact agreement for delta-scores were 74%, 81% and 91%, for synovitis, BML and osteophyte scores, respectively.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CI) were estimated to investigate the longitudinal associations between the change in MR-defined synovitis, BMLs or osteophytes (determinant) and change in joint pain on palpation (outcome) on joint level ($n = 8$ per patient), using generalized estimating equations (GEE) to account for the within patient effects. Additional adjustments were made for change in MR-defined synovitis, BMLs, and osteophytes, when appropriate; not for the other MR features, since these showed

no residual confounding effect. Because of the longitudinal study design with a fixed interval, we hypothesized that sex, age, body mass index (BMI) and follow-up time would have no confounding effects, which was confirmed through statistical assessment.

We selected painful joints with synovitis or BMLs present at baseline to test whether a decrease in synovitis or BMLs was associated with decreased joint pain scores; joints with stable or increased imaging scores served as the reference category.

We examined the contrary situation, selecting joints without maximum pain at baseline, to test whether an increase in MR-defined synovitis, BMLs, or osteophytes was associated with an increase in joint pain scores. For these analyses, joints with stable or decreased synovitis/BMLs/osteophytes served as reference category. Joints were selected regardless of baseline status of the MR feature under investigation, since our MR scoring protocol always allowed an increase in MR delta-scores. In addition, we repeated these analyses restricted to joints with the specific MR feature absent at baseline.

Subsequently, stratified analyses were performed for the associations of the three possible pairs of MR features with pain, while adjusting for the third feature, to explore the possibility of biological interaction (i.e., synergy or antagonism) in relation to joint pain. Interactions were evaluated as a departure from additivity of the per-stratum effects[30,31], and were quantified by attributable proportions with 95% CI, that were estimated by using the method described by Hosmer and Lemeshow[32], reflecting the proportion of the odds ratio for the doubly exposed group attributable to interaction. However, stratification led to a small number of joints per stratum and, combined with a high outcome-prevalence, this yielded infinitely large odds for the stratum of joints with an increase in both osteophytes and synovitis. Therefore, to attain a more sensible point estimate of the odds ratio and attributable proportion, we artificially added one joint without the outcome (i.e., one joint without an increase in pain) to this stratum.

Data were analysed using statistical package for the social sciences (SPSS) for Windows, version 23.0 (IBM SPSS statistics, New York, USA) and *P*-values <0.05 were considered statistically significant.

Results

Population

Of 105 HOSTAS patients with contrast enhanced MR images at baseline, only those with complete follow-up data were included in our analyses ($n = 85$). As depicted in Table I, the majority of patients fulfilled the ACR criteria, were middle-aged and female. Reasons for no follow-up after 2 years: 11 patients lost interest in study participation, five stopped after developing health problems (i.e., not hand OA), three skipped the 2-year visit because of health related issues (i.e., not hand OA), and one had fractured his right wrist, requiring a cast that impeded the examination of joint pain at the 2-year visit. Patients with and without follow-up did not differ at baseline (not shown). We studied a total of 680 hand joints from these 85 patients. Joints that could not be scored on either or both baseline and follow-up MR images, for example due to poor image quality or because they were outside the field of view, were excluded from analyses (synovitis $n = 10$, BMLs $n = 14$, osteophytes $n = 2$). While many joints remained stable over the 2 year interval, there was a substantial number of joints (Fig. 1) that had increased or decreased joint pain and MR feature scores (exact numbers in Supplementary Table S1). A small number of joints ($n = 13$) had decreased osteophyte-scores; however, assuming osteophytes are an irreversible feature, this was interpreted as measurement error and therefore these joints were deemed stable in further analyses on osteophytes.

Table I
Baseline characteristics of $n = 85$ patients with hand osteoarthritis (OA)

	Baseline	
Demographics		
Sex, *n* (%) female	69	(81.2)
Age, years	59.2	(7.3)
Fulfilling ACR criteria for hand OA, *n* (%)	76	(89.4)
Clinical assessment		
Body mass index, kg/m^2	27.1	(4.4)
VAS right hand pain, (0–100 mm scale)*	34	(22)
Tender joint count for right DIP/PIP joints, (0–8 scale)	1	(0–2)
Cylinder grip strength of right hand, kg	27.3	(12.7)
AUSCAN hand pain, (0–20 scale)	10	(7–12)
AUSCAN hand physical function, (0–36 scale)	15	(9–21.5)
Radiography (both hands)		
KL sum score for all hand joints, (0–120 scale)	18	(10.5–28)
Number of joints with KL score ≥2, (0–30 scale)	4	(1–9)
Osteophyte sum score for all hand joints, (0–58 scale)†	12	(6–17)
Erosive OA, *n* (%)	24	(28.2)
MR Imaging (right hand)		
Synovitis sum score, (0–24 scale)	7	(4–12)
Bone marrow lesions sum score, (0–24 scale)	2	(1–7)
Osteophytes sum score, (0–24 scale)	5	(3–10)

* $n = 84$ patients.
† Following OARSI atlas; Data are reported as mean (SD) or median (IQR), unless otherwise specified; ACR = American College of Rheumatology, AUSCAN = Australian/Canadian Hand Osteoarthritis Index, IQR = interquartile range, KL=Kellgren–Lawrence osteoarthritis grading scale, OARSI=Osteoarthritis Research Society International, SD = standard deviation, VAS = visual analogue scale.

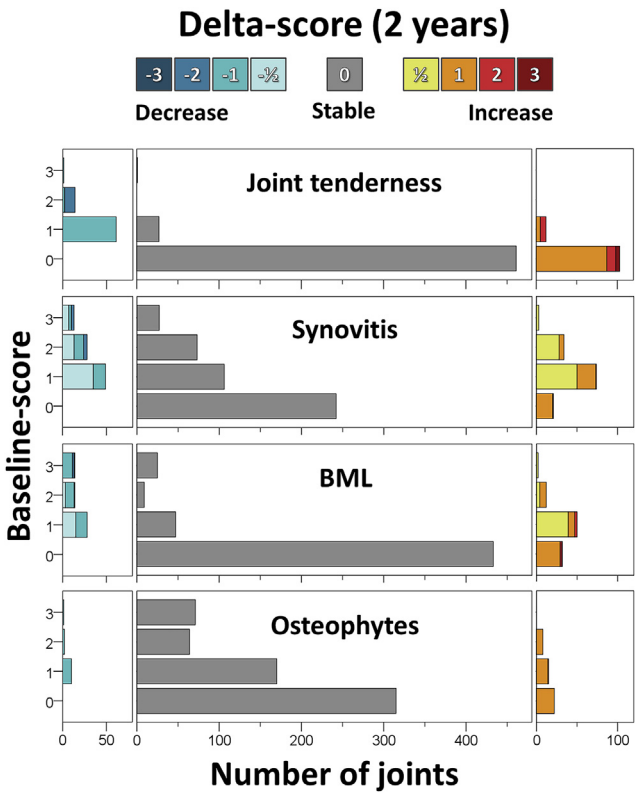

Fig. 1. Distribution of baseline and 2-year follow-up scores for 85 patients with hand osteoarthritis on joint level. Baseline scores for joint pain (*upper panels*, $n = 680$) and magnetic resonance (MR) features (*Second to fourth row*, $n = 670$, $n = 666$, and $n = 678$ respectively) are depicted on the *y*-axis, divided into decreased (*left panels*), stable (*middle panels*), and increased (*right panels*) delta-scores. Delta-scores are further specified through color-coding. Half-scores are only possible for change in synovitis and bone marrow lesion (BML).

Longitudinal associations between decrease in MR features and decrease in joint pain

Out of 116 joints with baseline pain, 76 had a reduced pain-score at follow-up, of which 73 had complete loss of pain. Synovitis decreased in 90 joints and BMLs in 56 joints (illustrative examples in Fig. 2). However, when the analysis was restricted to joints with baseline pain this was only 21 and 13 joints, respectively. In adjusted analyses, a decrease in synovitis, but not in BMLs, was associated with decreased pain scores (Table II). To rule out the possibility that misclassification of BML delta-scores obscured an existing positive association, we repeated the analyses restricted to joints with at least a whole point decrease in BML delta-score; however, this yielded similar results (data not shown).

Longitudinal associations between increase in MR features and increase in joint pain

Out of 678 joints without maximum pain at baseline, 115 had an increased score at follow-up, of which 103 had incident pain. An increase in synovitis, osteophytes, and, to a lesser extent, BMLs (illustrative examples in Figs. 2 and 3), was associated with

Fig. 2. Axial (*square panels*) and coronal (*rectangular panels*) fat saturated T1-weighted TSE with post-gadolinium enhancement (A, C) and fat saturated T2-weighted TSE (B, D) MR imaging showing changes in interphalangeal joints between baseline (*odd numbers*) and follow-up 2 years later (*even numbers*): decrease in synovitis in a fifth PIP joint (A); decrease in BML in a fifth DIP joint (B); increase in synovitis (C) and BML (D) in the same fourth DIP joint. The center of coronal images corresponds to the level of the axial images.

Table II
The associations between decreased MRI features and decreased joint pain (in joints with pain and MRI feature present at baseline)

	N/total (%) joints with decreased pain		Adjusted analyses* OR (95% CI)	Adjusted analyses† OR (95% CI)
Synovitis				
Stable/increase	30/58	(51.7)	1.0 (reference)	1.0 (reference)
Decrease	17/21	(81.0)	3.99 (0.95–16.8)	5.9 (1.12–31.0)
Bone marrow lesions				
Stable/increase	23/39	(59.0)	1.0 (reference)	n.a.
Decrease	6/13	(46.2)	0.39 (0.10–1.50)	n.a.

* Adjusted for patient effect.
† Adjusted for patient effect, increase of MRI-defined osteophytes, and decrease of BML/synovitis. OR=Odds ratio; CI = confidence interval; n.a. = not available, due to the low number of joints, it was not feasible to perform an analysis with further adjustments.

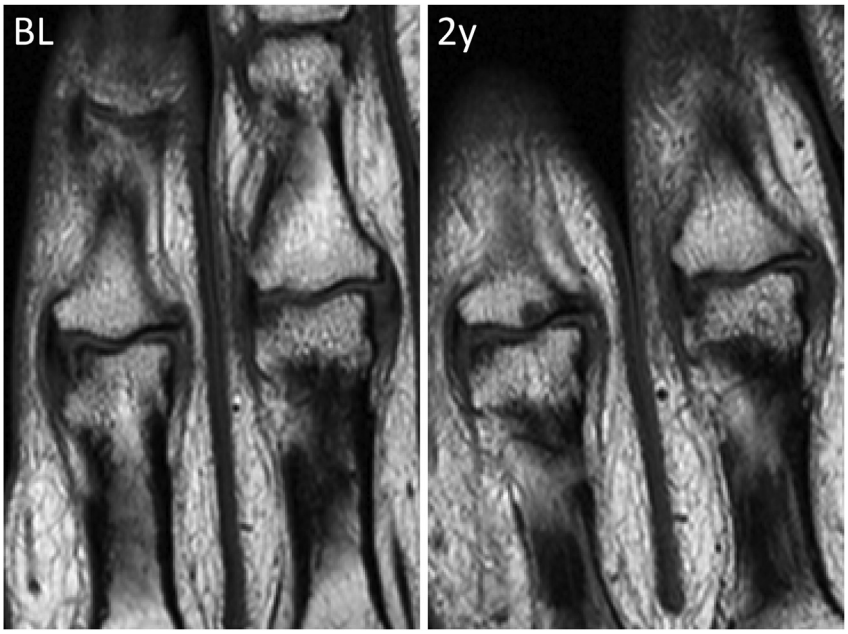

Fig. 3. Coronal T1-weighted TSE MR images demonstrating increase in size of osteophytes of the second and third PIP joints between baseline (BL) and follow-up 2 years later (2y).

increased pain (Table III). *De novo* synovitis and osteophytes, but not BMLs, showed even stronger associations with increased pain (Supplementary Table S2). After stratifying them for each other it became apparent that increase in synovitis and increase in osteophytes were the main effect modifiers, and that increased BMLs only had an effect through interaction, predominantly with synovitis (Fig. 4). The proportions of the total effect size in the doubly exposed groups due to biological interaction, quantified by attributable proportions (with 95% CI), were 0.47 (0.05–0.89) for synovitis × BMLs and 0.79 (0.51–1.07) for synovitis × osteophytes. The proportion attributable to the interaction between osteophytes and BMLs was small and not statistically significant (0.13; −0.69 to 0.94).

Discussion

For the first time we showed that in patients with primary hand OA, a decrease in MR-defined synovitis was strongly associated with a decrease in pain at the individual finger joint level over a 2-year period. A decrease in BMLs, contrary to our expectations, was

Table III
The associations between increased MRI features and increased joint pain (in joints without maximum pain at baseline)

	N/total (%) joints with increased pain		Adjusted analyses* OR (95% CI)	Adjusted analyses† OR (95% CI)
Synovitis				
Stable/decrease	78/536	(14.6)	1.0 (reference)	1.0 (reference)
Increase	36/132	(27.3)	1.80 (1.11–2.91)	1.81 (1.11–2.94)
Bone marrow lesions				
Stable/decrease	94/569	(16.5)	1.0 (reference)	1.0 (reference)
Increase	17/96	(17.7)	1.40 (0.99–1.97)	1.14 (0.81–1.60)
Osteophytes				
Stable	102/632	(16.1)	1.0 (reference)	1.0 (reference)
Increase	13/44	(29.5)	2.58 (1.53–4.4)	2.75 (1.59–4.8)

* Adjusted for patient effect.
† Adjusted for patient effect and increase of MRI-defined synovitis/BML/osteophytes. OR=Odds ratio; CI = confidence interval.

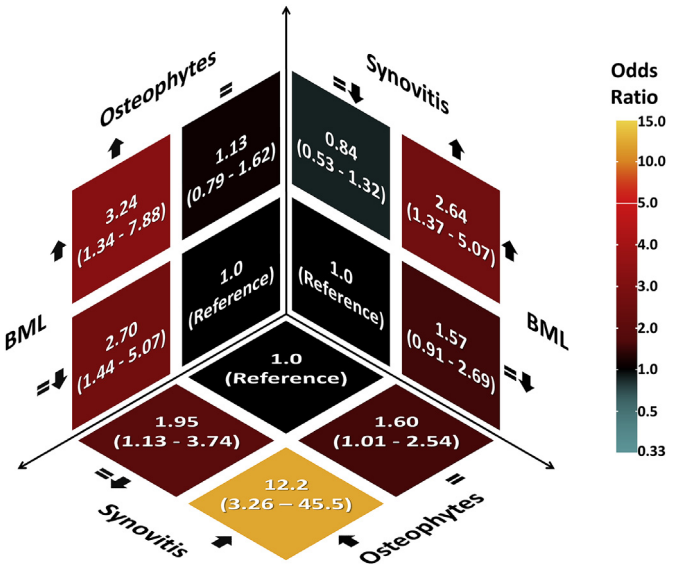

Fig. 4. Pairwise stratified analyses for the association between increase in MR features (independent variables) and increase in joint pain (outcome variable). Each plane represents one of three possible pairs: osteophytes × bone marrow lesions (BMLs), adjusted for synovitis (*left*); synovitis × BMLs, adjusted for osteophytes (*right*); synovitis × osteophytes, adjusted for BMLs (*bottom*). Data are odds ratios (95% confidence interval). BML; Increased MR feature (↑); decreased MR feature (↓); stable MR feature (=).

not associated with alleviation of pain. The relationship between change in synovitis and change in pain was supported by our observations for changes in the opposite direction: an increase in MR-defined synovitis or osteophytes was associated with increased joint pain.

In an earlier MR imaging study no association between decreasing synovitis and loss of joint pain was seen over a 5-year period[21]. However, a key consideration we took into account, was to select only joints that were 'at risk' of having both the determinant (i.e., the MR feature under investigation had to be present at baseline) and the outcome (i.e., pain had to be present at baseline), whilst in that previous study joints were selected solely based on baseline pain. Another possible explanation for the different outcome is the use of a shorter follow-up period: two instead of 5 years. While being long enough for synovitis and BMLs to change[33,34], it limits the possibility of peripheral neuronal or central pain sensitisation to take place or structural damage to develop. These processes can increase levels of joint pain[16,17] and would thus counteract the association of interest. Furthermore, the use of a more powerful MR unit (i.e., 1.5T vs 1.0T) with better spatial resolution could also add to the difference. The association found between increasing MR synovitis and pain is in line with the outcomes of previous cross-sectional[9–11,35] and longitudinal[12,21,33] finger OA imaging studies, that used different follow-up periods or other imaging modalities. However, we estimated smaller ORs for the association between increased MR synovitis and joint pain compared to the similar MR imaging study mentioned before[21], which could be due to us using a shorter follow-up time (i.e., 2 vs 5 years), restricting possible confounding by mechanisms already discussed above. Second, since we had 'increased joint pain' as outcome variable, we included all joints without maximum pain scores, instead of being limited to a subset of joints that were not tender at baseline, therefore we did not overestimate the effect size. Third, by scoring in random time order, we were not biased towards an assumption of worsening over time. Finally, we used a more powerful MR unit, which could detect smaller changes, therefore again preventing us from overestimation. Remarkably, in contrast to several cross-sectional studies[11,35,36] and one longitudinal study[21], we found that BMLs and pain are not directly associated in finger OA. However, in this longitudinal study we could demonstrate that BMLs act merely as effect modifier of, and just happen to be correlated with, change in synovitis and osteophytes. To more precisely characterize the role of the subchondral bone in OA – beyond the presence of BMLs – dynamic contrast-enhanced MR imaging could be used in future studies[37,38].

A strength of our study is that we show that already after 2 years, which could be the term of a clinical trial, a decrease in inflammation is associated with a decrease in an important outcome measure: pain. Moreover, this was shown in a varied population of patients with hand OA, which was not a selection of severe cases, but also included patients that did not (yet) fulfil the ACR criteria for hand OA. This is especially important, since the ACR criteria depend on the presence of hard tissue enlargements (i.e., osteophytes) which may only develop later in the disease course, while synovitis and BMLs might already be present in early disease stages. Hence, this a good representation of the target population – the 'average' patient with hand OA in secondary care – for whom treatment needs to be developed. Another important strength of our study is that we scored the MR images in random time order; a chronological time order could result in biased scoring, as readers might assume worsening over time. Although this might be a solid assumption for radiographic damage in hand OA[39], signs of inflammation as seen with ultrasonography or MRI can fluctuate over time and therefore progression cannot be assumed[21,34,40]. Our results showed that indeed this assumption cannot be made; synovitis and BMLs increased as well as decreased over 2 years. Therefore, we think that when scoring MR images over time, scoring in unknown time order should always be considered. When following the HOAMRIS score, simple rules (see methods) can be applied to prevent inflation of the score from a 4-point to a 7-point scale.

To reduce measurement error, we scored pairwise to be most sensitive to small changes within a joint/patient[41]. However, in combination with scoring in unknown time order, this also yielded a limitation: a small number of joints, less than 2 percent, decreased in osteophyte score. This is in line with another study scoring radiographs in unknown time order[42]. Since the general consensus is that osteophytes do not decrease over time, we interpreted decrease as measurement error. This misclassification could be attributed to the limited spatial resolution with our choice in slice thickness/gap, where small osteophytes could be missed, or to small differences in hand position during MR imaging between both visits, hampering test-retest reliability. A three-fold larger number of joints increased in osteophyte score, compared to decreased, indicating that there are 2-year changes beyond measurement error. Another methodological limitation is that while scoring, blinding for other features than the one that is scored, is impossible. In order to reach maximum possible blinding, we scored synovitis apart from the other features, using images from different MR sequences: axial T1 w-Gd for synovitis vs coronal and axial T1 w and T2 w images for the other HOAMRIS features. However, in a small interphalangeal joint with a lot of inflammation, it remains difficult to score features separately.

In conclusion, we demonstrated that a decrease in MR-defined synovitis is associated with reduced joint pain. Whether the reduction of inflammation in hand OA is clinically relevant, is an important question in the development of a treatment. Our results support the clinical relevance of targeting synovitis for treatment and are therefore of importance for hand OA clinical trials. Furthermore, they provide rationale behind the current recommendations to use, preferentially topical, non-steroidal anti-

inflammatory drugs in the treatment of symptomatic hand OA, as endorsed by the NICE, EULAR and ACR guidelines[7,43,44]. Future studies – ideally randomized controlled trials aimed at actively decreasing synovitis – are warranted to confirm our results, quantify effect sizes compared to a control group, and to elucidate how synovitis is targeted best.

Transparency declaration

Authors S van Beest and M Kloppenburg affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval information

Written informed consent was obtained from all participants. The study was approved by the LUMC medical ethics committee.

Author contribution

S van Beest designed the study, analysed the data, and drafted the manuscript.

W Damman designed the study, acquired data for the HOSTAS cohort, performed the MR imaging, scored the radiographs and MR images, and drafted the manuscript.

R Liu acquired data for the HOSTAS cohort, performed the MR imaging, and reviewed the manuscript.

FR Rosendaal was involved in data-analysis and reviewed the manuscript.

M Reijnierse was the supervising radiologist of the HOSTAS cohort, was involved in data-analysis, and reviewed the manuscript.

M Kloppenburg supervised the HOSTAS cohort, designed the study, was involved in data-analysis, and reviewed the manuscript.

Competing interest statement

All authors have completed the ICMJE uniform disclosure form and declare: we received financial support from the Dutch Arthritis Foundation: 10-1-405 for the MR imaging and LLP-24 for the Hostas cohort and appointment of authors S van Beest and W Damman; In the previous 3 years M Kloppenburg has received lecture fees/consultancy fees/fees as local investigator for industry driven trials from Pfizer, Abbvie, GlaxoSmithKline, Levicept, Merck, and grants (pending) from Pfizer, Dutch Arthritis Foundation, APPROACH-IMI (EU), OMERACT, EULAR.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplementary data

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