Lessons learnt about two-year follow-up in hand osteoarthritis: the HOSTAS study.

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BONE MARROW LESIONS AND SYNOVITIS ON MAGNETIC RESONANCE IMAGING ASSOCIATE WITH RADIOGRAPHIC PROGRESSION AFTER TWO YEARS IN HAND OSTEOARTHRITIS

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Abstract

Objective

To study the association of magnetic resonance (MR) features with radiographic progression of hand osteoarthritis over two years.

Methods

Of 87 primary hand osteoarthritis patients (82% women, mean age 59 years), baseline distal and proximal interphalangeal joint contrast-enhanced MR images were scored 0-3 for bone marrow lesions (BMLs) and synovitis following the Oslo score. Baseline and two-year follow-up radiographs were scored following Kellgren-Lawrence (KL) (0-4) and OARSI scoring methods (0-3 osteophytes, joint space narrowing [JSN]). Increase ⩾1 defined progression. Associations between MR features and radiographic progression were explored on joint and on patient level, adjusting for age, sex, BMI, synovitis and BML. Joints in end-stage were excluded.

Results

Of 696 analysed joints, 324 had baseline KL = 0, 28 KL = 4 and after two years 78 joints progressed. BML grade 2/3 was associated with KL progression (2/3 vs 0: adjusted RR [95% CI] 3.3 [2.1-5.3]) and with osteophyte or JSN progression, as was synovitis. Summated scores were associated with radiographic progression on patient level (RR crude BML 1.08 [1.01-1.2], synovitis 1.09 [1.04-1.1], adjusted synovitis 1.08 [1.03-1.1]).

Conclusion

BMLs, next to synovitis, show, already after two years, graded associations with radiographic progression, suggesting that both joint tissues could be important targets for therapy.

Introduction

The hand osteoarthritis (OA) disease process leads to joint destruction, visualized as radiographic damage[1]. With the need to develop effective therapies for hand OA, it is important to understand which processes are involved. By the time radiographic damage is visible, much of the disease process already took place[2]. Visualisation of the disease process in an earlier stage will facilitate identification of treatment targets and performance of clinical trials.

From ultrasonography studies in hand OA we know that synovial inflammation plays a role in radiographic progression[3–5]. MR has the advantage that subchondral bone can be visualised,[6] where bone marrow lesions (BMLs) are seen as increased water content in the trabecular bone, compatible with possible inflammation or bone fibrosis and remodelling[7,8]. In knee OA studies, BMLs were associated with structural progression[2,9]. In hand OA, one MR study (1.0 Tesla [T]) showed that BMLs, next to synovitis, could predict radiographic progression after 5 years[10]. However, clinical trials in hand OA measure outcome after one or two years follow-up, warranting more data on MR imaging[11].

As it is unclear whether underlying processes play the same role in onset (incident) and progression of radiographic osteoarthritic damage[2], we studied both together and apart for their association with baseline MR features. Next to the joint level, with summated MR scores we investigated progression on patient level, the level most clinically relevant. This study used for the first time a midterm follow-up of two years.

Materials and methods

Study design

We used data of HandOSTeoArthritis in Secondary care (HOSTAS), an observational cohort of consecutive patients from our outpatient clinic (a secondary and tertiary referral center enabling inclusion of patients in all disease stages), who were included after the clinical diagnosis of primary hand OA was made by their treating rheumatologist. The present analysis concerns patients who received contrast-enhanced MR imaging, included March 2011 to October 2012. 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 medical ethics committee. For clinical assessment see supplementary material.

Radiographs

Baseline and two-year follow-up radiographs of distal interphalangeal (DIP), proximal interphalangeal (PIP), interphalangeal (IP), metacarpophalangeal (MCP) and first carpometacarpal joints of both hands (30 joints per patient) were scored 0-4 following Kellgren-Lawrence (KL) scoring and 0-3 (IP 0-1) for osteophytes and joint space narrowing (JSN) following the OARSI atlas (MCP following the PIP atlas)[12,13]. Joints with the highest score or with arthroplasty were in end-stage. Reader WD scored paired in known order, blinded for demographic and clinical data. Intra-observer reliability (based on 10% of pairs) was high: cross-sectional intraclass correlation coefficients (ICCs) were 0.89-0.91 and longitudinal percentages exact agreement for progression 92-96% for the different methods.

Radiographic progression was defined as an increase in score above the smallest detectable change (SDC)[14]: SDCs on joint level 0.28-0.39, so ⩾1 grade defined progression. For sub-analysis, joints were classified as incident OA when they changed from no OA at baseline (KL score 0) to radiographic osteoarthritic damage (KL score 1-4). Joints progressed when they had signs of OA at baseline (KL score ⩾1) and increased in score.

Scores of KL (range 0-120), osteophytes or JSN (both 0-86) of all 30 hand joints were summated to study progression on patient level. SDCs were 2.2, 1.4 and 1.8, respectively. Therefore, increase ⩾3 grades in KL or ⩾2 grades in osteophyte or JSN summated scores defined progression.

MR imaging

MR imaging of the right DIP and PIP joints (n = 8 joints per patient) was performed at baseline, using an ONI-MSK-Extreme 1.5 T extremity MR imaging scanner (GE, Wisconsin, USA), acquiring coronal and axial T1-weighted pre-contrast and post-contrast injection and coronal and axial T2-weighted images (protocol in supplementary material). MR imaging scoring was performed blinded for demographic and clinical data by RL, using a modified version of the Oslo hand OA MR imaging scoring[15]. Cross-sectional intrareader reliability was high: ICC 0.84-1.00 (based on 11 patients). Synovitis and BMLs were scored 0-3, while effusion, flexor tenosynovitis (PIP joints) or flexor tendon involvement (DIP joints), extensor tendon involvement and cysts were scored present/absent (detailed scoring in supplementary material). BML and synovitis scores were summated (range 0-24) for patient level analysis.

Statistical analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) were estimated to study the association of MR features (determinant) with radiographic progression (outcome) on joint level using generalized estimating equations to account for the patient effect (joints within a patient as within-subject variable), while adjusting for age, sex and body mass index. An exchangeable working correlation matrix, a log link function and the Poisson distribution with robust standard errors were used[16]. Joints without the MR feature served as reference. BML or synovitis grades 2 and 3 were merged. Joints in radiographic end-stage at baseline were excluded, as they have no potential for progression. The association between summated scores of MR features (eight joints) and the presence of radiographic progression on patient level (both hands) was studied using the modified Poisson approach for binary data (i.e., a Poisson regression model with robust standard errors). Statistical software from SPSS for Windows, V.23.0 (IBM SPSS statistics, New York, USA) was used.

Results

Study population and prevalence of imaging features

Baseline MR imaging was performed in 107 patients, whereof 87 (83%) (82% women, mean age 59 years, follow-up time 2.1 years, supplementary material) had follow-up available. Reasons for no follow-up: 11 patients stopped, two were excluded, five skipped visit and two radiographs missed. Patients with and without follow-up did not differ (not shown).

At baseline, 28 (4%) joints were in end-stage for KL, 38 (6%) for osteophytes and 42 (6%) for JSN. Progression was seen in 12%, 9% and 10% of joints not in end-stage, respectively (supplementary material). At follow-up, one PIP joint had an arthroplasty and 25 patients showed no progression.

BMLs were present in 14.7% (102/693) of joints, while 41.4% (286/691) had synovitis, with missing data in three and five joints, respectively. Effusion, flexor or extensor tendon involvement or cysts were present in 8% (57/693), 3% (20/692), 7% (48/692) and 3% (23/696) of joints, respectively.

MR features and radiographic progression

BMLs grade 2/3 were associated with KL progression (vs 0 RR [95% CI] 3.3 [2.1-5.3]; Figure 1, supplementary material), while BML grade 1 was not. Synovitis showed graded

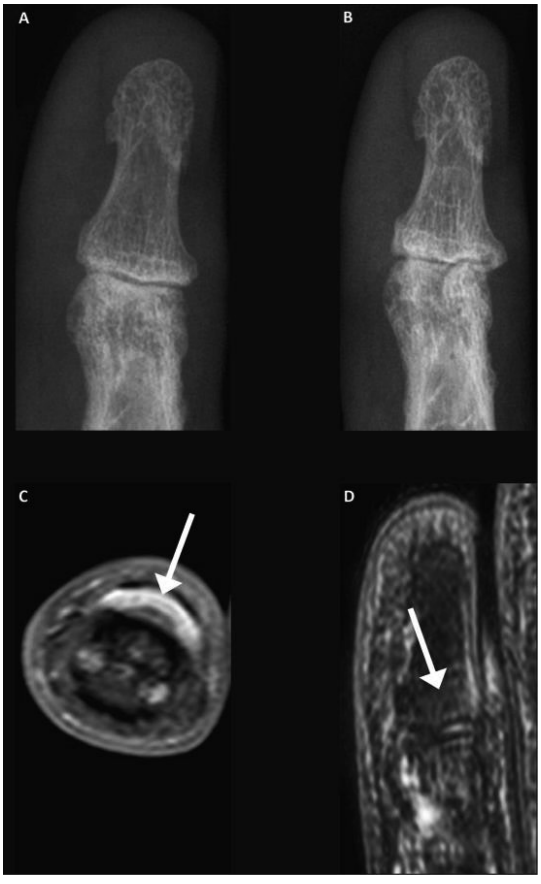

Figure 1. Radiographic progression of a second distal interphalangeal joint. Radiograph at baseline (A) and after two years (B) with corresponding magnetic resonance features (C and D) at baseline. (A) Dorsovolar conventional radiograph at baseline shows discrete joint space narrowing and subchondral cyst formation on the medial side. (B) Dorsovolar conventional radiograph after two years shows progression of joint space narrowing, subchondral cyst and osteophyte formation. (C) Axial T1-weighted fast spin echo (FSE) image with frequency selective fat suppression (FSFS) post-Gd at baseline shows synovial enhancement (synovitis grade 2) at the dorsal side (arrow). (D) Coronal T2-weighted FSE image with FSFS at baseline, shows high signal in the trabecular bone (bone marrow lesion grade 2) (arrow).

associations with KL progression. Similar results were found for associations with osteophyte and JSN progression (supplementary material). Adjustment for BMLs decreased the strength of the association between synovitis and progression, and vice versa. Neither effusion (present vs absent RR 0.8 [0.3-2.0]), nor flexor- (1.1 [0.2-5.9]), nor extensor tendon involvement (0.9 [0.3-2.5]) nor cysts (1.3 [0.5-3.3]) were associated with KL progression.

MR features and onset or progression of radiographic osteoarthritic damage

Of joints that increased in KL score, 33 had baseline KL = 0 (incident OA), while the other 45 joints had baseline KL≥1 (prevalent OA). Both BML and synovitis were associated with onset and progression and these associations were similar in strength (Table 1).

Table 1. Baseline Magnetic Resonance (MR) imaging features associated with radiographic progression in the same joint[#] after two years of follow-up in 87 patients with hand osteoarthritis in the HOSTAS cohort, stratified to the presence radiographic osteoarthritic damage at baseline.

(a) In 324 joints with no radiographic osteoarthritic damage at baseline (KL = 0), i.e., incident radiographic damage

MR feature (joint)	Number of joints with progression/ total (% progressed)	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
		KL incidence		
BML				
Grade 0, absent	29/309 (9)	1	1	1
Grade 1	2/12 (17)	1.9 (0.5 to 6.8)	2.0 (0.5 to 7.0)	1.6 (0.6 to 4.2)
Grade 2 + 3	2/3 (67)	6.8 (3.1 to 15.1)	8.8 (3.5 to 22.0)	4.3 (1.4 to 13.5)
Present	4/15 (27)	2.9 (1.2 to 7.2)	3.1 (1.3 to 7.3)	2.6 (1.4 to 5.0)
Synovitis				
Grade 0, absent	17/248 (7)	1	1	1
Grade 1	12/67 (18)	2.6 (1.4 to 5.0)	2.6 (1.4 to 5.0)	2.6 (1.4 to 5.0)
Grade 2 + 3	4/8 (50)	7.0 (3.0 to 16.1)	7.2 (3.1 to 16.7)	5.1 (2.1 to 12.3)
Present	16/75 (21)	3.1 (1.6 to 5.8)	3.1 (1.7 to 5.8)	3.0 (1.6 to 5.5)

(b) In 344 joints, not in end-stage, with progression of radiographic osteoarthritic damage (KL baseline 1-3).

		KL progression		
BML				
Grade 0, absent	25/273 (9)	1	1	1
Grade 1	8/51 (16)	1.8 (0.8 to 3.7)	1.7 (0.8 to 3.6)	1.3 (0.6 to 2.6)
Grade 2 + 3	11/17 (65)	7.2 (4.5 to 11.4)	7.3 (4.7 to 11.6)	3.5 (2.1 to 6.0)
Present	19/68 (28)	3.1 (1.9 to 5.1)	3.0 (1.8 to 4.9)	2.5 (1.5 to 4.1)
Synovitis				
Grade 0, absent	8/149 (5)	1	1	1
Grade 1	12/119 (10)	2.0 (0.8 to 4.9)	2.0 (0.8 to 5.0)	1.9 (0.8 to 4.7)
Grade 2 + 3	24/72 (33)	6.4 (2.9 to 13.8)	6.2 (2.8 to 13.6)	4.2 (1.8 to 9.9)
Present	36/191 (19)	3.6 (1.7 to 7.5)	3.5 (1.6 to 7.5)	3.0 (1.4 to 6.6)

*Model adjusted for age, sex and BMI. **Model adjusted for age, sex, BMI, BML and synovitis. [#]Due to no information, five and three joints were not taken into account in the synovitis and BML analysis, respectively. Joints in radiographic end-stage at baseline were excluded from the analysis, as they had no potential for progression. HOSTAS: Hand OSTeoArthritis in Secondary care; RR: risk ratio; KL: Kellgren-Lawrence; BML: bone marrow lesion; BMI: body mass index.

Table 2. Associations between summated scores of Magnetic Resonance (MR) imaging features and progression of radiographic osteoarthritis on patient level in 87 hand osteoarthritis patients*.

MR feature	KL progression (95% CI)	Osteophyte progression (95% CI)	JSN progression (95% CI)
Patients with progression/total	44/87	47/87	34/87
BML (0-24)			
Crude RR	1.08 (1.01 to 1.2)	1.05 (0.98 to 1.1)	1.11 (1.02 to 1.2)
RR adjusted for synovitis	1.00 (0.9 to 1.1)	1.01 (0.9 to 1.1)	1.00 (0.9 to 1.1)
RR adjusted age, sex and BMI	1.06 (0.99 to 1.1)	1.07 (0.98 to 1.2)	1.11 (1.01 to 1.2)
Synovitis (0-24)			
Crude RR	1.09 (1.04 to 1.1)	1.05 (1.004 to 1.1)	1.13 (1.1 to 1.2)
RR adjusted for BML	1.09 (1.04 to 1.2)	1.05 (0.99 to 1.1)	1.12 (1.05 to 1.2)
RR adjusted age, sex and BMI	1.08 (1.03 to 1.1)	1.07 (1.02 to 1.1)	1.14 (1.1 to 1.2)

*RRs should be interpreted as increased risk per point increase in summated BML or synovitis scores. For example, our observed range for summated BML score was 0-10, so patients with the highest BML score have a 1.08^{10} = 2.16 times (216%) higher risk for KL progression than patients without any BML. KL: Kellgren Lawrence; JSN: joint space narrowing; BML: bone marrow lesion; RR: risk ratio; BMI: body mass index.

Summated MR features and progression on patient level

Median (range) summated BML score was 1 (0; 10) and synovitis score was 4 (0; 13). Both BML and synovitis summated scores were crudely associated with progression. However, after adjustment, only the associations for synovitis remained statistically significant (Table 2).

Discussion

MR imaging-defined BMLs, like synovitis, showed dose-response associations with radiographic progression in hand OA already after two years, confirming earlier studies on ultrasound-detected synovitis[3], but indicating that BMLs in hand OA, like in knee OA[2,9], are an important additional factor in the disease process. Also, because the presence of BMLs decreases the strength of the association between synovitis and progression, and vice versa.

A strength of our study is inclusion of patients in all disease stages from early to severe. Other cohorts have patients with hand OA that are more severely affected with more joints in end-stage at baseline;[3,10] these joints have no potential for onset of OA or progression and are thus excluded from the analysis.

Another strength is the distinction in onset and progression of radiographic damage in individual hand joints. Of note, this distinction resulted in few joints in some groups and

therefore results should be interpreted with caution. We used a cut-off at doubtful to definite OA (KL 1), since lesions can already be present at KL = 1. Like in knees, where KL = 1 at baseline was a strong predictor for progression and considered as early-stage OA[17]. We showed that both BML and synovitis were associated with onset and progression and that these associations were similar in strength. This is in line with results for ultrasound-detected synovitis[4], but was not described before in MR-detected BMLs and synovitis.

Novel is our approach to investigate progression on patient level, which is most relevant from a clinical perspective. Summated BML or synovitis score showed crude associations with progression, although only for synovitis this remained statistically significant after adjustment. This means that the more severe the inflammatory state is, the higher the risk of progression in both hands. We hypothesise that inflammatory MR imaging features could be modified by anti-inflammatory medication like steroids. Future proof-of-concept randomized controlled trials could explore this hypothesis.

This is the first study using 1.5 T MR scanner in hands, enabling more precise identification of lesions with a higher signal-to-noise ratio compared with 1.0 Tesla. Consequences are indicated by our results: we found an association between JSN progression and synovitis grade 1, where another hand OA MR study using 1.0 T did not[10].

Our study also had some limitations and restrictions in interpretation of results. First, we did not have information whether MR imaging features are persistent or fluctuating. Especially persistent or progressing lesions have shown to be associated with progression and onset of OA[3,18,19] Nevertheless, we already found the association with only one time measurement. Another limitation is the number of patients in our study. However, the circumstance that in every patient eight joints can be studied provided enough power to study associations with progression.

Our study indicates that all joint tissues, including BMLs, are important in the disease course of hand OA and it illustrates the use of MR imaging, visualising BMLs, in detecting early-stage hand OA and detection of joints and patients prone to progress. Future studies should focus on the persistent or fluctuant nature of BMLs in hands and on hand MR imaging in the short term.

References

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Supplementary material

MRI protocol

MR imaging was performed using an ONI-MSK-Extreme 1.5 T extremity MR imaging scanner (GE, Wisconsin, USA). The right hand DIP and PIP joints (n = 8 joints) of each patient were examined, regardless of clinical features or dominance.

The following sequences were used: coronal T1-weighted (T1-w) fast spin echo (FSE) images (repetition time [TR]/echo time [TE] 575/11 milliseconds [ms], acquisition matrix [AM] 388 × 288, echo train length [ETL] 2, minimum TE), axial T1-w FSE images (TR/TE 500/10.2 ms, AM 340 × 288, ETL 2, minimum TE), coronal T2-w FSE images with frequency selective fat saturation (FSFS) (TR/TE 3000/61.8 ms, AM 300 × 224, ETL 7) and axial T2-w FSE images with FSFS (TR/TE 3000/57 ms, AM 336 × 192, ETL 7) before contrast injection, and coronal T1-w FSE images with FSFS (TR/TE 600/10.4 ms, AM 364 × 224, ETL 2, minimum TE) and axial T1-w FSE images with FSFS (TR/TE 650/7.7 ms, AM 320 × 192, ETL 2, minimum TE) after intravenous injection of gadolinium-chelate (Gd; gadoteric acid, Guerbet, France, standard dose 0.1 mmol/kg). Coronal images had a field of view (FOV) of 120 mm and 18 slices with slice thickness 2 mm and slice gap 0.2 mm. Axial sequences had a FOV of 100 mm and 24 slices with slice thickness 3 mm and slice gap 0.3 mm. Total acquisition time was 30 minutes.

MRI scoring

MR imaging scoring was performed using a modified version of the Oslo hand OA MR imaging scoring. Effusion and extensor tendon involvement (see definition) were added to the scoring. Since there is no tendon sheet around the extensor tendon on DIP and PIP joint level or around the flexor tendon on DIP joint level*, we renamed tenosynovitis to involvement.

BMLs, synovitis, flexor tenosynovitis and cysts were scored in the same manner as described in the atlas, using T2-weighted images instead of STIR. Data for flexor pathology were dichotomized in presence and absence after scoring.

Synovitis was defined as an area in the synovial compartment showing post-Gd enhancement (on T1-w post-Gd images) of a thickness greater than the width of synovium (≥1 mm). Score 0 = no synovitis; 1 = mild, 1/3 of synovium thickened; 2 = moderate, 2/3 thickened; 3 = severe, all synovium thickened.

BMLs were defined as lesions within the trabecular bone with signal characteristic consistent with increased water content on T2-w images: 0 = no BML, 1 = 1-33% of bone

with BML, 2 = 34%-66% with BML, 3 = 67%-100% with BML. Distal and proximal joint sites were scored separately and the highest score was taken as the score for the whole joint.

Effusion, fluid in the joint, was present when an area showed increased signal intensity on T2-w images, non-enhancing on T1-w post-Gd images and only when synovitis was present.

Flexor tenosynovitis (PIP joints) or flexor tendon involvement (DIP joints) was present when an area in the flexor tendon (sheath) showed post-Gd enhancement on T1-w images more than normally expected.

Extensor tendon involvement was present when opposite sides of the tendon showed post-Gd enhancement on T1-w images more than normally expected.

Cysts were defined as sharply marginated bone lesions without a cortical break with low signal on T1-w pre-Gd images and high signal on T2-w images.

*Nieuwenhuis WP, Krabben A, Stomp W, et al. Evaluation of Magnetic Resonance Imaging–Detected Tenosynovitis in the Hand and Wrist in Early Arthritis. Arthritis Rheumatol 2015;67(4):869–876.

Clinical assessment

Demographic and disease characteristics were collected by standardized questionnaires. Self-reported hand pain was assessed by visual analogue scale (range 0-100 millimeter). Self-reported hand function (0-30) was assessed by the Functional Index for Hand OsteoArthritis (FIHOA)*. Higher scores indicate worse health.

Physical examination was performed by a trained research nurse, assessing the distal interphalangeal (DIP), proximal interphalangeal (PIP), interphalangeal, metacarpophalangeal (MCP) and first carpometacarpal joints of both hands (n = 30 joints per patient) for tenderness upon palpation and bony and soft swelling.

* Wittoek R, Vander Cruyssen B, Maheu E, et al. Cross-cultural adaptation of the Dutch version of the Functional Index for Hand Osteoarthritis (FIHOA) and a study on its construct validity. Osteoarthritis Cartilage 2009;17(5):607–12.

Supplementary table 3. Baseline characteristics of 87 hand osteoarthritis (OA) patients with available contrast-enhanced magnetic resonance imaging at baseline and follow-up radiographs from the HOSTAS cohort.

Patient level, 87 patients	
Age, mean (SD), years	59.4 (7.6)
BMI, mean (SD), kg/m^2	27.3 (4.4)
Women, number (%)	71 (82)
Self-reported symptom duration, median (range), years	5.5 (0.3 to 36.8)
Dominance, n (%)	
Right	63 (72)
Unclear	8 (9)
Fulfilling ACR criteria*, number (%)	80 (92)
VAS pain, mean (SD), 0-100^	
Right hand	33.6 (21.4)
Left hand	33.9 (22.5)
Self-reported function, median (range), 0-30	8 (0 to 24)
Median number of involved joints per patient (range)	
Tender joints upon palpation 0-30	3 (0 to 24)
Bony swellings 0-30	12 (0 to 22)
Soft swellings 0-30	0 (0 to 17)
Radiographic erosive disease**, n of patients (%)	26 (30)
Joint level, 696 joints (n = 8 per patient)	
Physical exam findings, n/total (%)	
Tenderness upon palpation	120/696 (17)
Bony swelling	420/696 (60)
Soft swelling	49/696 (7)

*Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–10. ^n = 86. **Erosive disease was present when having ≥1 joint with an eroded or remodelled subchondral plate following Verbruggen-Veys anatomical phase scoring (Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308–20). BMI: body mass index; ACR: American College of Rheumatology; VAS: visual analogue scale.

Supplementary table 4. Baseline Magnetic Resonance (MR) imaging features associated with radiographic progression in the same joint[#] after two years of follow-up in 87 patients with hand osteoarthritis in the HOSTAS cohort.

MR feature (joint)	Number of joints with progression/ total (% progressed)	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
		Kellgren-Lawrence progression		
BML				
Grade 0	54/582 (9)	1	1	1
Grade 1	10/63 (16)	1.7 (0.8 to 3.3)	1.6 (0.8 to 3.2)	1.2 (0.7 to 2.1)
Grade 2 + 3	13/20 (65)	6.9 (4.7 to 10.1)	7.2 (4.9 to 10.6)	3.3 (2.1 to 5.3)
Synovitis				
Grade 0	25/397 (6)	1	1	1
Grade 1	24/186 (13)	2.1 (1.2 to 3.6)	2.2 (1.3 to 3.7)	2.1 (1.2 to 3.6)
Grade 2 + 3	28/80 (35)	5.6 (3.4 to 9.3)	5.7 (3.4 to 9.5)	4.0 (2.2 to 7.1)
		Osteophyte progression		
BML				
Grade 0	41/577 (7)	1	1	1
Grade 1	9/61 (15)	2.0 (0.8 to 4.9)	2.0 (0.8 to 4.8)	1.4 (0.7 to 3.0)
Grade 2 + 3	10/17 (59)	7.9 (4.4 to 14.2)	8.7 (5.0 to 15.1)	3.7 (2.2 to 6.4)
Synovitis				
Grade 0	15/397 (4)	1	1	1
Grade 1	23/182 (13)	3.6 (1.9 to 7.1)	3.6 (1.8 to 7.3)	3.4 (1.7 to 6.8)
Grade 2 + 3	22/74 (30)	8.3 (4.5 to 15.4)	8.3 (4.2 to 16.1)	5.7 (3.0 to 11.1)
		Joint space narrowing progression		
BML				
Grade 0	46/580 (8)	1	1	1
Grade 1	11/60 (18)	1.8 (0.8 to 3.9)	1.8 (0.8 to 3.9)	1.3 (0.6 to 2.8)
Grade 2 + 3	9/11 (82)	7.7 (4.3 to 13.8)	7.8 (4.2 to 14.5)	3.5 (1.7 to 7.2)
Synovitis				
Grade 0	20/394 (5)	1	1	1
Grade 1	23/184 (13)	2.3 (1.3 to 4.1)	2.3 (1.3 to 4.1)	2.1 (1.1 to 3.9)
Grade 2 + 3	23/71 (32)	5.5 (2.9 to 10.6)	5.5 (2.7 to 11.1)	3.5 (1.7 to 7.4)

[#]Due to no information, 3 and 5 joints were not taken into account in the BML and synovitis analysis, respectively. *Model adjusted for age, sex and BMI. **Model adjusted for age, sex, BMI, BML and synovitis. The JSN analysis was also adjusted for presence of baseline JSN (score ⩾1). Joints in radiographic end-stage at baseline were excluded from the analysis, as they had no potential for progression. BML: bone marrow lesion; RR: risk ratio; BMI: body mass index; JSN: joint space narrowing.