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

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BONE MARROW LESIONS ON MAGNETIC RESONANCE IMAGING IN HAND OSTEOARTHRITIS ARE ASSOCIATED WITH PAIN AND INTERACT WITH SYNOVITIS

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Abstract

Objective

To determine the association between bone marrow lesions (BMLs) and (teno)synovitis as assessed on magnetic resonance (MR) imaging in patients with pain in hand osteoarthritis (OA).

Methods

In 105 consecutive patients with primary hand OA (83% women, mean age 59 years), who were diagnosed by rheumatologists and included in the HOSTAS (Hand OSTeoArthritis in Secondary care) cohort, contrast-enhanced MR imaging (MRI) of right distal and proximal interphalangeal joints were obtained. In 92 patients joint site specific pain upon palpation was assessed within 3 weeks of MRI examination. MR features were scored (0-3) following the Oslo hand OA score: BMLs, synovitis, cysts, and flexor tenosynovitis. Additionally, extensor tendon inflammation was scored (0-3). Odds ratios (OR, 95% CI) were calculated using generalized estimating equations for MR features with joint pain, adjusted for putative confounders. Stratified analyses were performed to investigate interaction.

Results

BMLs, synovitis, cysts, flexor tenosynovitis and extensor tendon inflammation were demonstrated in 56%, 90%, 22%, 16% and 30% of patients, respectively. BMLs (grade 2/3 vs 0: 3.5 [1.6-7.7]) and synovitis (3 vs 0: OR 3.6 [95% CI 1.9-6.6]) were severity-dependent associated with joint pain, but flexor tenosynovitis and extensor tendon inflammation were not. Stratified analyses showed that BMLs did not associate with pain in the absence of synovitis, whereas synovitis was associated with pain in the absence of BMLs. Interaction was seen between BMLs and synovitis grade 2 or 3.

Conclusion

In patients with hand OA, severe synovitis is associated with joint pain, which is worsened when BMLs co-occur, suggesting synovitis as primary target of treatment.

Introduction

Hand osteoarthritis (OA) can result in a high clinical burden. Especially hand pain can lead to a decreased quality of life[1]. Knowledge of the underlying pain mechanisms in hand OA enables optimal treatment of hand pain. Many ultrasonography studies in patients with hand OA demonstrated that synovial inflammation is present in hand OA and plays a role in the presence of hand pain. Tenosynovitis of the flexor tendon is also present in hand OA and associated with hand pain[2,3], but the involvement of the extensor tendon is unknown.

Magnetic resonance imaging (MRI) studies have indicated that in the subchondral bone of osteoarthritic joints ill-defined areas of high signal intensity can be visualized on fat-suppressed T2 weighted or short tau inversion recovery (STIR) sequences, so-called bone marrow lesions (BML)[4]. Histologically BMLs represent mainly areas of fibrosis, necrosis and trabecular bone abnormalities[5]. In knee OA these BMLs have been widely investigated and play a role in knee pain[6]. BMLs in hand OA have been rarely studied. In two studies of patients with late stage hand OA the presence of BMLs has been demonstrated[2,3]. Haugen et al. showed an association between BMLs and hand pain, both cross-sectionally and longitudinally[2,3,7].

Since no data of BMLs in patients in earlier stages of hand OA are available, we set-up a study to determine their prevalence in patients presenting themselves to our Rheumatology outpatient clinic. It is unclear how BMLs relate to synovitis in osteoarthritic hand joints and therefore we do not know whether synovitis or BMLs are crucial in hand pain. Hence we investigated their co-occurrence and interaction with respect to pain, to be able to determine which target is most promising to alleviate pain. This is also important, since imaging synovitis is difficult due to the need for contrast enhanced MR imaging, which adds cost, complexity and risk to the MR imaging protocol. We also investigated whether extensor tendon inflammation plays a role in hand OA.

Materials and methods

Study design

Cross-sectional data were used of the HOSTAS (Hand OSTeoArthritis in Secondary care) study, an ongoing cohort. This cohort enrolled consecutively diagnosed patients with hand OA since 2009 to investigate determinants of outcome in hand OA. Patients were included when they consulted a rheumatologist at the outpatient clinic of the Leiden University Medical Center (LUMC) for hand complaints and these hand complaints were diagnosed as

primary hand OA. Exclusion criteria include any other pathological condition that could explain existing symptoms, secondary OA and routine MRI-contraindications. For the present analysis, only patients were included who received a contrast enhanced MRI (CE-MRI). Written informed consent was obtained from all participants. The study was approved by the LUMC medical ethical committee.

Demographics and clinical characteristics

Standardized questionnaires were used to collect demographics and clinical characteristics. Participants underwent standardized physical examination of their hands by a trained research nurse. All distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), first interphalangeal (IP) and first carpometacarpal (CMC) joints were evaluated for site-specific pain upon palpation (0-30, additive scale)[8].

Self-reported pain

Pain intensity in the right hand was measured by a pain visual analogue scale (VAS). Furthermore, the Michigan Hand Outcomes Questionnaire (MHQ) pain subscale was filled in (5-point Likert scale and normalization to 0–100, higher scores = greater pain)[9]. Also the pain subscale of the Australian Canadian Hand OA Index (AUSCAN) in its Likert format was acquired[10]. Both MHQ and AUSCAN assess hand pain in both hands simultaneously.

Mental health

Subscales of the 36-item Short Form Health Survey (SF-36) were measured to calculate the mental health component score. This component score was standardized using data based on the norms from the Dutch population[11,12].

MR imaging

From March 2011 to October 2012, MR imaging was performed as part of the baseline examination of the patients included in HOSTAS, using an ONI-MSK-Extreme 1.5 Tesla (T) extremity MR imaging scanner (GE, Wisconsin, USA), with a dedicated 100 mm coil. The right hand DIP and PIP joints (n = 8) 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, standard dose 0.1 mmol/kg).

Coronal images had a field of view of 120 mm and 18 slices with a slice thickness of 2 mm and a slice gap of 0.2 mm. Axial images had a field of view of 100 mm and 24 slices with a slice thickness of 3 mm and a slice gap of 0.3 mm. Total acquisition time was 30 min.

MR imaging scoring was performed by one dedicated well-trained reader (RL) (supervised by radiologist MR with more than 20 years of experience) using a modified version of the Oslo hand OA MR imaging scoring system[13] (Figure 1). Scoring was performed blinded for demographic and clinical data.

Synovitis was defined as an area in the synovial membrane that showed post-Gd enhancement of a thickness greater than the width of normal synovium (>1 mm)[13] on T1-w images and seen on at least two consecutive slices. Scoring was based using thirds of the maximum potential volume of enhanced synovial tissue (0 = normal, 1 = mild, 2 = moderate and 3 = severe).

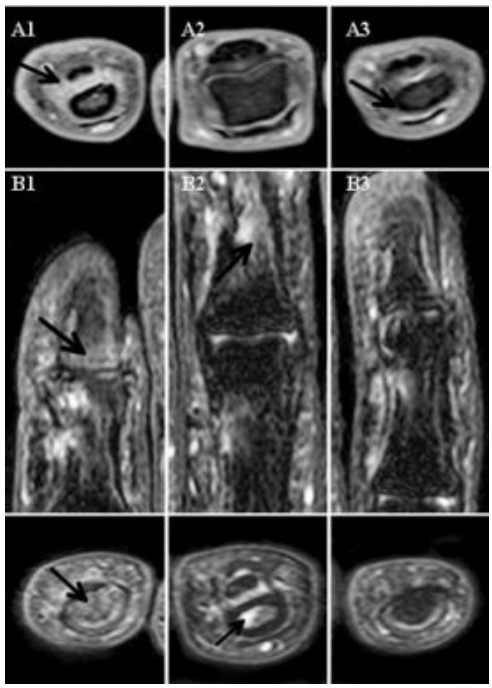

Figure 1: Axial (A) T1-weighted FSE images with frequency selective fat saturation (FSFS) post-gadolinium enhancement, axial (C) and coronal (B) T2-weighted FSE images with FSFS MR imaging of the same patient: Synovitis (A1) and bone marrow lesion (BML, B1, C1) were present in the painful second distal interphalangeal joint. A non-painful third proximal interphalangeal joint with BML (B2, C2) and no synovitis (A2). Synovitis (A3) without the presence of BML(B3, C3) in the painful fourth distal interphalangeal joint.

Flexor tenosynovitis was defined as an area in the flexor tendon sheath that showed post-Gd enhancement of a thickness greater than the normal width of the tendon sheath (as shown in the Oslo atlas) on T1-w images, visible on at least two consecutive slices and involving the entire tendon sheath by being circumferential. Scoring occurred as follows: 0 = normal, 1 = <0.5 tendon thickness, 2 = ⩾0.5 and <1 tendon thickness, 3 = ⩾1 tendon thickness.

Extensor tendon inflammation was defined as an area in the extensor tendon that showed enhancement of a thickness greater than the normal width of the tendon, is visible on at least two consecutive slices and when opposite sides of the extensor were enhanced. Scoring was performed according to the same scoring method as the flexor tendon: 0 = normal, 1 = <0.5 tendon thickness, 2 = ⩾0.5 and <1 tendon thickness, 3 = ⩾1 tendon thickness.

BMLs at distal and proximal joint site were defined as lesions within the trabecular bone with signal characteristics consistent with increased water content and ill-defined margins on T2. The distal and proximal part of the joint was scored separately for the proportion of bone with BML: 0 = no BML, 1 = 1-33 % of bone with BML, 2 = 34-66 % of bone with BML, 3 = 67-100% of bone with BML. The highest score was taken as the BML score for the whole joint.

Cysts (0-1; absent or present) at distal and proximal joint site were defined as sharply marginated bone lesions with typical signal characteristics (Low signal intensity on T1 pre-gadolinium and high signal intensity on T2), which is visible in two planes without a cortical break.

One of the authors (RL) re-scored 11 randomly selected MR scans after at least 3 weeks, and the intrareader reliability for synovitis, flexor tenosynovitis, BML and cyst was high (intraclass correlation coefficient [ICC] ⩾0.97), while the ICC for extensor tendon inflammation was intermediate (ICC 0.76).

Radiographs

Conventional radiographs of the hands (dorso-volar) were obtained. The DIP joints, PIP joints, first IP joints, MCP joints and first CMC joints were scored by one of the authors (WD). The Kellgren-Lawrence (KL) grading scale (0-4, maximum score 120) was used for the scoring of structural osteoarthritic damage and the Verbruggen-Veys anatomical phase scoring was used for erosion (N-S-J-E-R depicted as 0-1-2-3-4, maximum score 120). Joints were considered erosive when they were in phase E (erosive) or R (remodelled). The dedicated well-trained scorer (WD) (supervised by MK with more than 10 years of

experience in scoring hand radiographs) was blinded for clinical and demographic data. Intrareader reproducibility, taking in account the severity of the score, depicted by the ICC was assessed on a randomly selected sample (n = 31) of radiographs and was high (ICC for KL 0.91 and for Verbruggen-Veys 0.86).

Statistics

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using generalized estimating equations (GEEs) to investigate the association between MR imaging features with site specific pain upon palpation in DIP and PIP joints while adjusting for age, sex, body mass index (BMI) and patient effect. Additionally, ORs with 95% CIs were calculated with logistic regression for the association between summated MR imaging scores and self-reported pain, with adjustment for age, sex, BMI, mental health and KL score. The cut-off for the VAS pain, MHQ pain and AUSCAN pain was the median. Furthermore, a stratified analysis was performed to investigate BMLs and the effect of synovitis in site specific pain upon palpation. If more than 3 weeks elapsed between the time of MR imaging and physical examination, the data were excluded from this analysis.

Results

Study population

In 105 patients (83% women, median age 59.4 years, 91% fulfilled the American College of Rheumatology criteria for hand OA)[14]. MR imaging was obtained from 840 joints of the right hand (Table 1). In eight DIP and PIP joints of the right hand, the median number of hand joints with a KL grade of at least 2 was 2 (0-8) and the percentage of erosive hand OA was 23%. Due to technical problems, in three and four joints no BMLs or synovitis could be scored respectively. Other features such as cysts could be evaluated in all joints.

In 92 patients physical examination was performed within 3 weeks of the MR imaging and the association between MR imaging features with hand pain was analysed. Patient and clinical characteristics from these 92 patients did not differ from the total population of 105 patients (data not shown).

Prevalence of BMLs, synovitis, tendon inflammation and cysts

BMLs were present in 56% of the 105 patients and synovitis in 90%. Abnormalities in tendons were found less often: flexor tenosynovitis in 16%, while extensor tendon inflammation was seen in 30%. Cysts were seen in 22% of the patients (Table 2). BMLs

Table 1. Baseline characteristics of 105 consecutive hand osteoarthritis (OA) patients diagnosed at an outpatient clinic of rheumatology.

Variable*	Patients with hand OA (n = 105)
Age, yrs	59.4 (40.4-79.9)
Female sex, n (%)	87 (83)
BMI	26.9 (17.6-40.7)
Symptom duration, yrs	5.3 (0.33-36.8)
ACR criteria hand OA, n (%)	95 (91)
Radiographic hand OA**, n of patients (%)	92(88)
Assessment of 8 scanned joints	
-erosive hand OA, n of patients (%)#	24 (23)
-Number of joints with KL≥2	2 (0-8)
-Number of site specific painful joints upon palpation	1 (0-8)
Self-reported symptoms	
VAS pain right hand, mm	36 (0-83)
VAS pain left hand, mm	34 (0-83)
AUSCAN pain (0-20)	10 (0-20)
MHQ pain (0-100)	45 (0-95)

*Median (range) unless otherwise stated. **At least one joint with Kellgren-Lawrence score ≥2. #At least one erosive interphalangeal joint in the right hand. Eight joints: DIP and PIP joints right hand. BMI: body mass index; VAS: visual analogue scale; MHQ: Michigan Hand outcomes Questionnaire; ACR: American College of Rheumatology

Table 2. Prevalence of MR imaging features in distal and proximal interphalangeal joints of the right hand in 105 patients with hand osteoarthritis.

MR imaging feature	Patients with hand OA (n = 105)
Joint	
Bone marrow lesion	
Patients, n (%)	59 (56)
Joints, median (range)	1 (0-6)
Synovitis	
Patient, n (%)	94 (90)
Joints, median (range)	3 (0-8)
Flexor tendon	
Tenosynovitis	
Patient, n (%)	17 (16)
Joints, median (range)	0 (0-4)
Extensor tendon	
Tendon inflammation	
Patient, n (%)	31 (30)
Joints, median (range)	0 (0-8)
Cyst	
Patients, n (%)	23 (22)
Joints, median (range)	0 (0-3)

were preferentially seen in DIP 2, 3 and PIP 2, synovitis in DIP 2, 3 and PIP 2 through 5, flexor tenosynovitis in PIP 3 and extensor tendon inflammation in PIP 5 (Figure 2).

Association between MR imaging features and site specific pain upon palpation in right DIP and PIP joints

736 joints in the 92 patients were available for the investigation of the association between MR imaging features and pain. After adjustment for age, sex, BMI and patient effect, BMLs and synovitis were associated with pain in the site specific joint upon palpation (Table 3). Flexor tenosynovitis, extensor tendon inflammation and cyst in the tendons were not associated with pain upon palpation in the joint. On conventional radiographs, structural osteoarthritic damage, as characterized by KL grade of at least 2, was also associated with pain (Table 3).

Additional analyses including BML and synovitis together in the multivariate analyses showed associations for BMLs (grade 2+3 vs 0: OR 3.5 [1.6-7.7]) and synovitis (grade 3 vs 0: OR 3.6 [95% CI 1.9-6.6]). The associations between BMLs or synovitis with pain remained after adjustment for structural damage in the joint. Structural damage was characterized by a KL score of at least 2. When KL score was added to the analyses, KL score was no longer statistical significantly associated after adjustment for BMLs and synovitis (Table 3).

Figure 2: Prevalence (percentage of patients) of MR imaging features in all proximal and distal interphalangeal joints of the right hand in 105 consecutive patients with hand osteoarthritis diagnosed at a rheumatology outpatient clinic.

Interaction between BMLs and synovitis in their association with site specific pain upon palpation

BMLs and synovitis often co-occurred. This co-occurrence could conceal their relative contribution in the association with site specific pain upon palpation. Therefore, a stratified analysis was performed to investigate BMLs and the sole effect of synovitis in site specific pain upon palpation and to elucidate potential interaction between BMLs and synovitis. Seven percent (n = 54) of the hand joints were painful upon palpation in the absence of both BMLs and synovitis. In 231 hand joints, synovitis was present while BMLs were absent. When grade 3 synovitis was present without BMLs (n = 20), seven joints (35%) were painful upon palpation. BMLs, both small and moderate/severe lesions, were seldom present when synovitis was absent (33 joints of 416 joints without synovitis had a BML grade 1 and only one joint had a BML grade 2/3); BMLs did not have an effect on pain in the absence of synovitis. In joints where BMLs and moderate and severe synovitis (grade 2 or 3) co-occur (n = 49), 26 (53%) of these joints were painful upon palpation. The associations between MR imaging features and pain in the different strata are depicted in Table 4 and examples are shown in Figure 1. In the joints with moderate synovitis (grade 2) the co-occurrence with BMLs resulted in an increased risk for site specific pain upon palpation when compared with joints without BMLs [5.1 (2.1-12.2) instead of 1.2 (0.4-3.2)] (Table 4). While the basic risk for site specific pain upon palpation for sole BMLs or moderate synovitis is 1 (background risk = 1 + 0.2 [synovitis risk] – 0.2 [BML risk]), whereas the risk for co-occurrence of synovitis grade 2 and BMLs is 5.1; therefore a clear interaction can be demonstrated. In joints with severe synovitis (grade 3) a comparable interaction is seen: the basic risk for site specific pain upon palpation for sole BMLs or severe synovitis is 2.1 (background risk = 1 + 1.3 [synovitis risk] – 0.2 [BML risk]). Whereas the risk for site specific pain upon palpation for the co-occurrence of severe synovitis and BMLs is 6.9. Adjustment for KL grade did not change these interactions (data not shown).

Association between MR imaging features and self-reported pain

No association was seen between the summated score of MR imaging features and self-reported VAS pain of the right hand, AUSCAN pain and MHQ pain (data not shown).

Table 3. Association between MR imaging features and 736 distal and proximal interphalangeal joints assessed for site specific pain upon palpation in 92 patients with hand osteoarthritis.

	Pain joint present/absent	Adjusted OR (95% CI) *	Adjusted OR (95% CI) **	Adjusted OR (95% CI) ***
Joint				
BML				
Grade 0	96/518	1.0	1.0	1.0
Grade 1	20/67	1.5 (0.9-2.5)	1.2 (0.7-2.2)	1.1 (0.6-2.0)
Grades 2+3	18/14	6.3 (2.9-13.8)	3.5 (1.6-7.7)	3.1 (1.4-7.1)
Synovitis				
Grade 0	59/357	1.0	1.0	1.0
Grade 1	36/178	1.2 (0.8-1.8)	1.1 (0.8-1.7)	1.1 (0.7-1.6)
Grade 2	18/40	2.6 (1.4-4.6)	1.9 (1.01-3.6)	1.8 (0.96-3.6)
Grade 3	20/24	5.4 (2.8-10.4)	3.6 (1.9-6.6)	3.2 (1.7-6.3)
Flexor tendon				
Tenosynovitis				
Grade 0	130/585	1.0		
Grade 1	3/14	0.7 (0.2-2.4)		
Extensor tendon				
Inflammation				
Grade 0	121/568	1.0		
Grade 1	12/31	1.3 (0.6-3.0)		
Cyst				
Grade 0	130/584	1.0		
Grade 1	4/18	1.0 (0.4-2.6)		
Structural damage				
Kellgren-Lawrence				
<2	76/447	1.0		1.0
≥2	55/150	2.1 (1.4-3.0)		1.3 (0.9-2.0)

*Adjusted for age, sex, BMI and patient effect. **Multivariate model with age, sex, BMI, patient effect, synovitis, and BMLs. ***Multivariate model with age, sex, BMI, patient effect, synovitis, BMLs and Kellgren-Lawrence score (<2 vs ≥2). BMI: body mass index, BML: bone marrow lesion.

Table 4. Odds ratios (with 95% CIs)* of site specific pain upon palpation by synovitis status and the presence or absence of bone marrow lesions (BMLs) in 732 joints of 92 patients with hand osteoarthritis.

	No synovitis	Synovitis		
		Grade 1	Grade 2	Grade 3
	n = 416	n = 214	n = 58	n = 44
BMLs absent	1 (background) n = 382	1.2 (0.8-1.8) n = 178	1.2 (0.4-3.2) n = 33	2.3 (0.96-5.7) n = 20
BMLs present	0.8 (0.2-2.8) n = 34	1.3 (0.6-3.2) n = 36	5.1 (2.1-12.2) n = 25	6.9 (2.7-17.7) n = 24

*Adjusted for age, sex and body mass index. n: number of joints.

Discussion

In 840 interphalangeal joints from 105 patients with hand OA, BMLs, (teno)synovitis, tendon inflammation and cysts were frequently seen. Both BMLs and synovitis were associated with site specific pain upon palpation. Novel in this study is that BMLs alone were not associated with pain, whereas severe synovitis alone was, and that a clear interaction between BMLs and synovitis was seen. In 53 % of joints with BMLs and moderate to severe synovitis, site specific pain upon palpation was observed, resulting in a nearly 7-fold increased risk for pain when compared with interphalangeal joints without BMLs or synovitis. This is an important finding, identifying synovitis as primary possible target in future therapeutic options.

Though previous MR imaging studies in hand OA have been scarce, knee OA has been the topic of extensive research. Features such as BMLs and synovitis are often associated with pain in such studies[6,15-17]. It is possible that a similar interaction between the two features also exists in knee OA and may explain the inconsistency of the results. Unfortunately, further distinction between the two features and its possible interaction has not been investigated as we have done with our study.

Neither flexor tenosynovitis nor extensor tendon inflammation nor cysts were associated with pain. Flexor tenosynovitis was investigated previously and was associated with pain, when only corrected for age and sex[3]. We could not replicate these results. A possible explanation lies in a difference of study population and differences in the methods of the studies. The prevalence (median = 1) of joints with flexor tenosynovitis and the number of painful joints (median = 4) in the other study was higher while patients were older (mean = 68.8)[3]. To our best knowledge, this is the first study to report on the presence of extensor tendon inflammation in hand OA. The anatomic absence of a tendon sheath and close relation with the joint made us question whether a direct relationship between extensor tendon inflammation and joint pain would be present. This MR feature was found in a third of the patients. Though no association was found between extensor tendon inflammation and pain, it is possible that this feature is associated with other clinical properties, such as hand mobility. More studies will be needed to further investigate this feature.

Our study also has its limitations. We have employed a modified version of the hand OA MR imaging scoring system, a system developed in recent years. However we used a 1.5 T MR systems, which would produce different images than the 1.0 T systems used to develop the initial score. Based on previous studies in OA, we have incorporated

additional features such as extensor tendon inflammation to further investigate our own understanding of the association between MR imaging features and clinical signs of OA.

Since insertion sites of the deep and superficial parts of the flexor and extensor tendons differ between DIP and PIP joints, it could be useful to analyse these groups of joints separately. Due to low numbers this was not possible in our study.

The reliability of the MRI scorings yielded mostly good results for the features investigated in our study. The ICC for extensor tendon inflammation was lower than the other features, but still performed better when compared with the ICC of flexor tenosynovitis in another MRI study[13]. Future studies will be necessary to investigate if extensor tendon inflammation is perhaps a more difficult feature to define or the definition needs further adaptation.

The study population consists of a relatively large proportion of women (83%). Hand OA occurs more often in women than in men[18]. This could explain the high female participation rate in both our study group and in a previous MR Imaging study for hand OA where 91% of the study population consisted of women[3].

Our results illustrate the advantages of MR imaging over radiographs and ultrasonography. Features such as BMLs and synovitis offer better agreement with the clinical assessment of a patient. We have found that the presence of BMLs and synovitis on joint level are both independently associated with site specific pain upon palpation, when corrected for age, sex, BMI, KL-grade and patient effect. BMLs and synovitis are not associated with self-reported pain on the patient level, which may be explained by an inability to correct for the individual patient effect. Pain is subjective and it will be challenging to discover which known and unknown variables will all contribute to the patient effect. We hypothesized that mental health may explain this patient effect, but this was not the case. The involvement of the carpometacarpal joint may be another one of such variables, as previous study has shown that this joint contributes more to pain than interphalangeal joints. Unfortunately, we could not further test our theories due to lack of information[19].

References

1 Kloppenburg M and Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol.* 2012;8:22-31.

2 Wittoek R, Jans L, Lambrecht V, Carron P, Verstraete K, Verbruggen G. Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI. *Ann Rheum Dis.* 2011;70:278-283.

3 Haugen IK, Boyesen 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.

4 Haugen IK and Hammer HB. Role of modern imaging techniques in hand osteoarthritis research and clinical practice. *Curr Rheumatol.* Rep 2014;16:399.

5 Del GF, Farahani SJ, Carrino JA, Chhabra A. Bone marrow lesions: A systematic diagnostic approach. *Indian J Radiol Imaging.* 2014;24:279-287.

6 Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis.* 2011;70:60-67.

7 Haugen IK, Slatkowsky CB, 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;75:702-708.

8 Bijsterbosch J, Wassenaar MJ, le CS, Slagboom PE, Rosendaal FR, Huizinga TW et al. Doyle Index is a valuable additional pain measure in osteoarthritis. *Osteoarthritis Cartilage.* 2010;18:1046-1050.

9 Chung KC, Pillsbury MS, Walters MR, Hayward RA. Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. *J Hand Surg Am.* 1998;23:575-587.

10 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;10:863-869.

11 Ware JE, Jr. and Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473-483.

12 Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol.* 1998;51:1055-1068.

13 Haugen IK, Lillegraven S, Slatkowsky-Christensen B, Haavardsholm EA, Sesseng S, Kvien TK et al. Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. *Ann Rheum Dis.* 2011;70:1033-1038.

14 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;33:1601-1610.

15 Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis Cartilage.* 2006;14:1033-1040.

16 Kornaat PR, Kloppenburg M, Sharma R, Botha-Scheepers SA, Le Graverand MP, Coene LN et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol.* 2007;17:3073-3078.

17 Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann Rheum Dis.* 2007;66:1599-1603.

18 Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage.* 2005;13:769-781.

19 Bijsterbosch J, Visser W, Kroon HM, Stamm T, Meulenbelt I, Huizinga TW et al. Thumb base involvement in symptomatic hand osteoarthritis is associated with more pain and functional disability. *Ann Rheum Dis.* 2010;69:585-587.