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Evaluating the Relation between Bone Marrow Lesions and Synovitis with Pain and Structural Damage in Hand Osteoarthritis

Nidhi Sofat and Soraya Koushesh

Abstract

Osteoarthritis (OA) is the most prevalent arthritis worldwide and is a condition affecting the whole joint. Changes in subchondral bone, cartilage integrity and synovitis are recognised during OA progression. Although advances have been made in our understanding of OA pathophysiology, there are no current treatments that delay or halt the progression of the disease. Treatments are largely based upon physical therapies to improve function, anti-inflammatory agents for pain symptoms and joint replacement surgery for late stage disease in large weight bearing joints. There is an urgent need to better understand the pathophysiology of OA that could translate into improved treatments for this condition. In recent years, more advanced imaging techniques including magnetic resonance imaging (MRI) have led to an improved understanding of changes at the bone-cartilage interface in OA, with recognition that loss of integrity at the cartilage-bone junction and development of bone marrow lesions (BMLs) in the subchondral bone are associated with OA pain in large epidemiological studies. In this book chapter, we review the evidence for the role of BMLs and synovitis, particularly in the pathophysiology of hand OA. Based on a systematic review of the literature, we have identified 15 articles reported on BMLs and synovitis in hand OA, which will be discussed in this chapter.

Keywords: hand osteoarthritis, bone marrow lesions, synovitis, joint space narrowing, osteophytes, pain

1. Introduction

Osteoarthritis (OA) is the most common debilitating arthritis worldwide, with a preponderance for affecting the knee, hip, hand, spine and feet. It is a leading cause of physical disability and pain in our ageing populations worldwide. The rising epidemic of obesity is also contributing to the increasing incidence of OA, with a greater impact on the quality of life of sufferers and healthcare costs in many systems worldwide [1].

In large epidemiological cohorts of OA, hand OA (HOA) in particular causes a significant disease burden. The Framingham Study reported hand OA to have a prevalence of 27.2% [2]. The same study reported that women were more likely to develop hand OA symptoms in comparison to men [3]. In a large European study of

7983 people, 25% of participants with hand pain showed significant hand disability, with 24.2% of subjects reporting OA of any joint and 28.3% subjects having a manual occupation [4]. Such studies demonstrate the significant symptom burden and functional impairment that hand OA places in human populations worldwide.

Pain and loss of function in OA are as a result of pathological changes in the entire joint structure. Specifically in hand OA, structural changes leading to pain and functional impairment include cartilage damage, subchondral bone sclerosis, subchondral cysts, synovitis, osteophyte formation, erosions and bone marrow lesions (BML) [5]. In the clinic, underlying joint damage can be observed clinically as joint deviation and deformity, swelling e.g. formation of distal interphalangeal (DIP) and proximal interphalangeal (PIP) joint swelling and loss of function [5]. In addition to DIP and PIP joint involvement in hand OA, the thumb first carpometacarpal (CMC) joint can also be involved, which functionally can cause severe functional impairment (**Figure 1**). Although mechanical factors with manual occupations are a major risk factor for hand OA, other factors including increasing age and obesity contribute significantly to disease burden [6].

Current therapies for hand OA include improving physical function and strengthening exercises [7], supportive aids including taping devices [8] and pain management [9]. Pain relieving agents currently include topical or oral therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics and capsaicin [10]. Intra-articular therapies include corticosteroids and hyaluronic acid in suitable cases [11]. Since there are currently no proven disease-modifying therapies for hand OA, there is a huge unmet need to better understand disease pathophysiology, which could lead to the development of improved therapies for hand OA.

Imaging studies in recent years have provided useful insights into the pathophysiology and progression of hand OA [12]. Historically, imaging of the hand in OA has favoured plain radiography (**Figure 1**), but more recently US and MRI have been used in clinical studies to evaluate radiographic changes in HOA. Modalities of imaging used have included plain radiography and magnetic resonance imaging (MRI). Plain radiography is consistently able to identify a number of structural

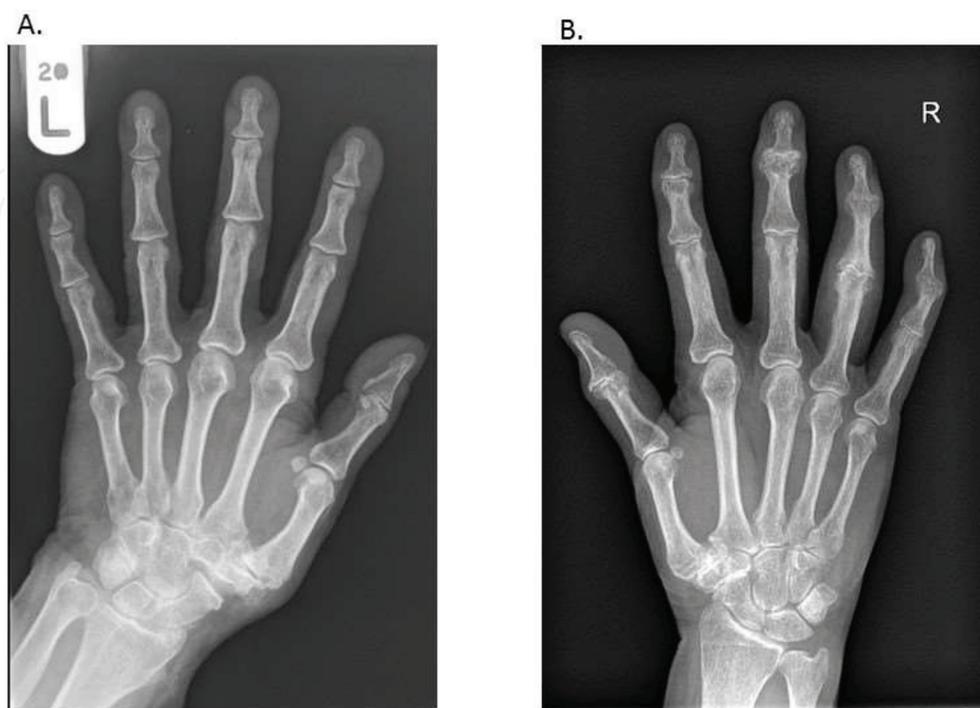


Figure 1. Plain radiographic changes in hand osteoarthritis due to thumb first carpometacarpal joint involvement (A) and proximal and distal interphalangeal joint involvement (B).

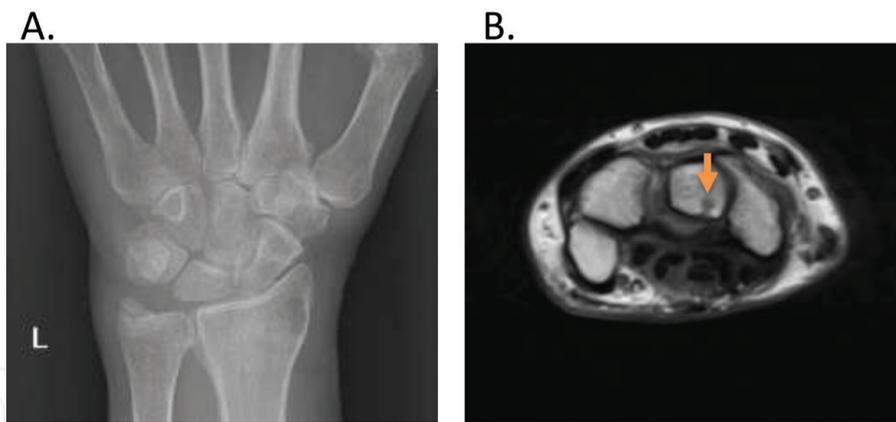


Figure 2. Correlation of plain radiographic changes with MRI bone marrow oedema. (A) Wrist joint showing early joint space narrowing and sclerotic changes. (B) Bone marrow oedema in carpal bone on corresponding MRI scan of the wrist in the same patient (arrow).

changes such as joint space narrowing and osteophyte formation [13]. However, other joint tissue structures including synovitis and subchondral bone marrow lesions, which are linked to pain, may not be easily visualised by plain radiography.

Numerous cross-sectional studies have proposed radiographic features to be strongly associated with pain and functional impairment [14] which may be better visualised by MRI evaluation for hand OA [15]. MRI has now become widely accepted as a reliable imaging modality for identifying bone marrow lesions (BML) (see **Figure 2**) and synovitis in OA [16], with a large number of studies already conducted in knee OA [17]. With respect to the hand, fewer clinical and imaging correlative studies have been conducted. Studies conducted in the Oslo hand OA cohort has shown MRI features, including BML and synovitis, to be strongly associated with joint tenderness, making these potential targets for future treatments [18, 19].

Although several studies have now been published with respect to radiographic changes including BMLs, cartilage damage and synovitis associated with structural progression and pain in knee OA in particular, there is no systematic review reporting hand structural changes including MRI, synovitis and cartilage damage in hand OA. In this chapter we sought to summarise existing knowledge on studies evaluating BML, cartilage damage and synovitis in hand OA specifically, since these structural changes are associated with pain in hand OA. We aimed to investigate the most frequent imaging modalities reported in the published literature, which included plain radiography and MRI.

2. Search strategy for systematic review

A systematic literature search was conducted through the following electronic databases: Pubmed (from 1996), EMBASE via Ovid (from 1996), Medline via Ovid (from 1996) and Web of Science via Ovid (from 1970) to June 2018. The inclusion criteria for keyword searches were: bone marrow lesion(s) (BMLs), osteoarthritis (OA), imaging, synovitis, and pain. We included studies that observed the associations between BMLs, synovitis, osteophytes and the development of osteoarthritis pathophysiology under magnetic resonance imaging. Initially, it was agreed to conduct a systematic review comprising of all joints affected by osteoarthritis. After careful search, we found that no previous authors had summarised imaging studies on the progression of BMLs and/or synovitis in HOA by systematic review. We agreed to summarise all available literature in HOA relating clinical features to imaging findings to date by systematic review. For exclusion criteria,

the search strategy results were screened through the titles by two reviewers NS and SK. Studies were excluded if they were: reviews, letters to the editor, case reports, case series or studies which were not in the English language. All searches were restricted to human subjects. No limits were applied to the sex and age of the subjects. Both reviewers independently screened through the abstracts to exclude any irrelevant articles and eligible full articles were obtained to further analyse the criteria for review. Studies were eligible if they examined BMLs, synovitis and other structural changes using imaging techniques in participants with hand OA. Following the initial search, studies reporting data on hand OA only were included in the systematic review reported herein.

3. Results

3.1 Data extraction

The literature flow is depicted by using the Preferred reporting items for Systematic reviews and Meta-Analyses (PRISMA) diagram in **Figure 3**. Following database searches, 2831 articles were extracted for title screening. Following exclusion of duplicate studies and obvious exclusions, 2796 papers were removed and the remaining 35 studies were selected for abstract screening.

Of the 35 studies selected for screening, 19 did not meet the inclusion criteria (bone marrow lesion(s), osteoarthritis, imaging, synovitis, and pain). Full text articles were obtained for 15 studies and independently reviewed by the same two reviewers (NS and SK) for relevance and quality. Following full text review, one study was removed as it was the abstract of a full publication already included for review. A total of 15 studies were included in this systematic review. The data extracted from each study included: country of study, number of participants, structural changes, type of MRI scanner used and pain scores assessed. A summary of the studies and their demographics is shown in **Table 1**. The structural changes described by each study is summarised in **Table 2**.

3.2 Study characteristics

The mean age for all studies was 64.4 [18–32]. Most studies (n = 13) were performed on both genders, although the majority of the subjects in each study were female. Only two studies [26, 32] had female subjects only and one study did not report the gender of the participants [25]. Of these studies, 13 were from observational cohort studies: the Hand OSTeoarthritis in secondary care (HOSTAS) [27, 29–31] the Oslo hand OA cohort [18–23, 25, 32] and a clinical trial: the digital osteoarthritis in refractory hand OA (DORA) study [28]. All articles examined BMLs and various subchondral features using MRI. The strength of the magnetic field was 1.5 T in four studies [27, 29, 26, 30]. Eight studies used a 1.0 T system [18–23, 25, 32] whereas one study [28] used the 0.2 T system in two patients only. Only one study used a 3.0 T system [24] while one study did not report the MRI system used [31].

3.3 Data from cohort observational studies

In the HOSTAS study, 87 subjects with primary hand OA were included, of which 82% were women [27]. All participants had radiographic measures and MRI scans conducted, with Kellgren-Lawrence grading (KL) (0–4) and OARSI grading methods [osteophytes 0–3, joint space narrowing (JSN)] for radiographic severity collected. Radiographic progression over the 2-year period was considered as

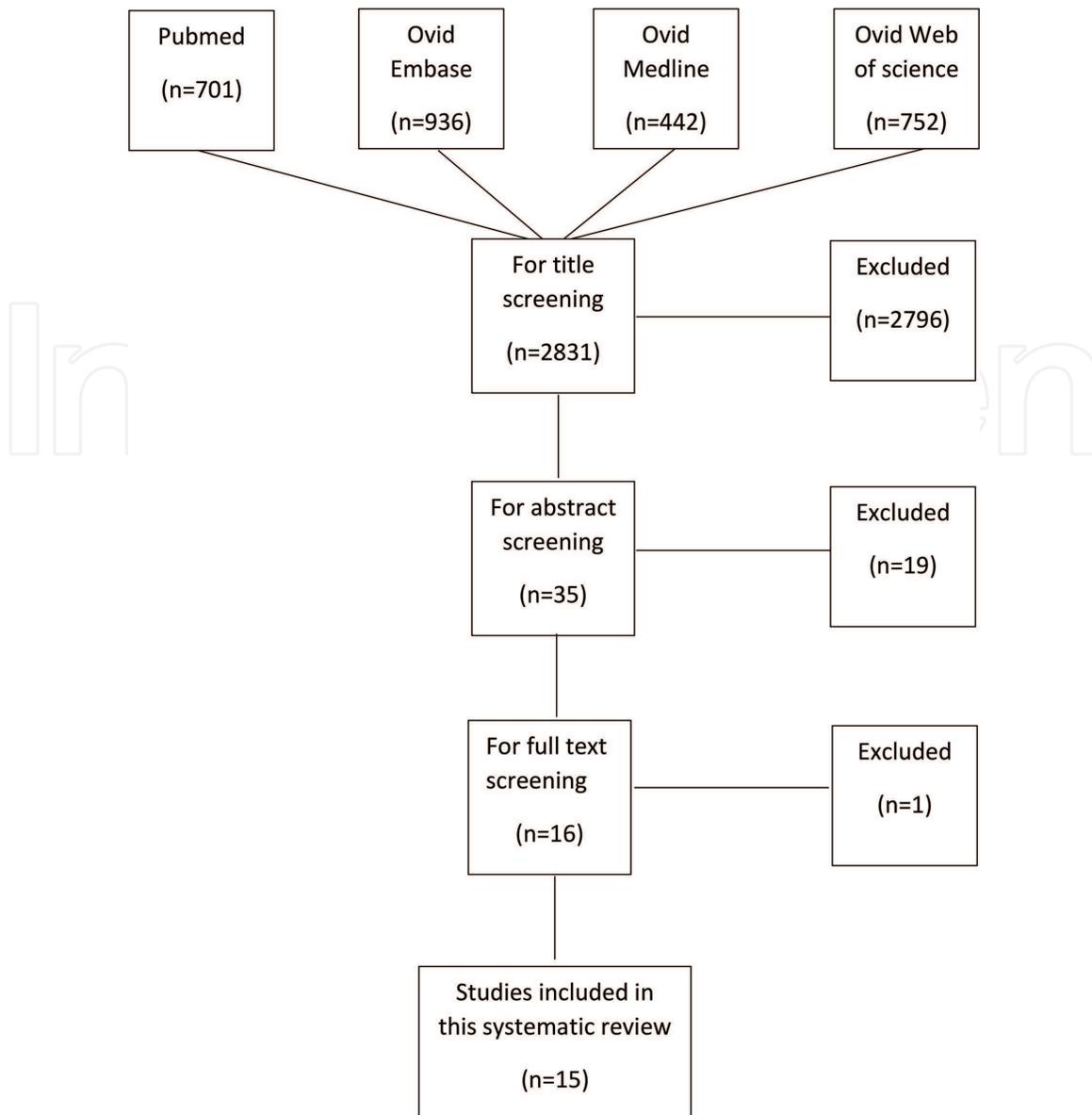


Figure 3.
 PRISMA flow diagram for systematic review.

an increase in score of ≥ 1 . Associations between MR features and radiographic progression were explored after adjusting for age, sex, body mass index (BMI), synovitis and BML. The group analysed 696 joints in their study, to find that BMLs and synovitis were both associated with radiographic progression by plain radiography and MRI. In comparing plain radiographic versus MRI changes, BMLs grade 2/3 were associated with KL progression, while BML grade 1 was not. Synovitis also showed graded associations with KL radiographic progression.

A number of studies have been reported by the Oslo Hand OA cohort, which was initially established in 2001. This cohort underwent extensive evaluation from 2001 to 2003, with further follow-up from 2008 to 2009. A number of observations of pain and functional characteristics in relation to imaging scores have been reported in this cohort. In their first report, Haugen et al. [18] reported the associations between MRI features and measures of pain and physical function in hand OA. Eighty-five participants (77 women) with mean age 68.8 (5.6) years underwent contrast-enhanced MRI of the interphalangeal joints (dominant hand) and clinical joint assessment. One investigator read the MRIs for presence/severity of changes including osteophytes, joint space narrowing, erosions and BMLs. A reliable scoring system previously developed by the authors was used to assess changes [20].

Publication	Number of participants and mean age	Country	Clinical outcome measures	Imaging modalities measured
Haugen et al. [18]	85 (91% women) Mean age = 68.8	Norway (Oslo HOA)	AUSCAN FIHOA AIMS-2 Grip strength	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [19]	70 (90% women) Mean age = 67.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [20]	10 (90% women) Mean age = 69.5	Norway (Oslo HOA)	Not applicable	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [21]	106 (92% women) Mean age = 68.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [22]	70 (90% women) Mean age = 67.9	Norway (Oslo HOA)	AUSCAN Grip strength	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Haugen et al. [23]	74 (91% women) Mean age = 67.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI
Kortekaas et al. [24]	16 [13 with erosive hand] (62% women) Mean age = 57.0	Norway	Pain assessed during physical examination	Plain radiograph 3.0 T MRI Ultrasound
Haugen et al. [25]	20 (95% women) Mean age = 65.8	Norway (Oslo HOA)	AUSCAN	Plain radiograph 1.0 T MRI
Ramonda et al. [26]	11 (100% women) Mean age = 59.0	Italy	AUSCAN VAS Dreiser FIHOA	Plain radiograph Kellgren-Lawrence Scoring 1.5 T MRI
Damman et al. [27]	87 (82% women) Mean age = 59.0	The Netherlands (HOSTAS)	Not applicable	Plain radiograph Kellgren-Lawrence Scoring 1.5 T MRI
Roux et al. [28]	18 (77.8% women) Mean age = 64.4	France (DORA)	VAS Dreiser FIHOA	Plain radiograph Kellgren-Lawrence Scoring 0.2 T MRI (2 patients)
Liu et al. [29]	105(83% women) Mean age = 59.4	The Netherlands (HOSTAS)	AUSCAN VAS SF-36 MHQ	Plain radiograph Kellgren-Lawrence Scoring 1.5 T MRI
Kroon et al. [30]	289 (83% women) total - 202 (84% women) = MRI subjects - 87 = Ultrasound subjects (excluded from review) Mean age = 60.1	The Netherlands (HOSTAS) (LUMC)	AUSCAN VAS	Plain radiograph MRI 1.5 T Ultrasound

Publication	Number of participants and mean age	Country	Clinical outcome measures	Imaging modalities measured
Kroon et al. [31]	524 (86% women) Mean age = 61.9%	The Netherlands (HOSTAS)	AUSCAN VAS SF-36 HADS	Plain radiograph Kellgren-Lawrence Scoring MRI system not reported
Wolski et al. [32]	21 (100% women) Mean age = 69.9	Norway (Oslo HOA)	AUSCAN	Plain radiograph Kellgren-Lawrence Scoring 1.0 T MRI

Table 1.
Publications included in systematic review by clinical outcome and imaging measures.

Publication	Structural changes
Haugen et al. [18]	BML, synovitis, flexor tenosynovitis, osteophytes, erosions, attrition, malalignment
Haugen et al. [19]	BML, synovitis
Haugen et al. [20]	BML, synovitis, flexor tenosynovitis, osteophytes, jsn, erosions, malalignment, cysts, collateral ligament
Haugen et al. [21]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, malalignment, cysts, erosion, attrition
Haugen et al. [22]	BML, synovitis, erosion, central erosion
Haugen et al. [23]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, malalignment, cysts, erosion, attrition, collateral ligament
Kortekaas et al. [24]	BML, synovitis, osteophytes, JSN, erosion
Haugen et al. [25]	BML, synovitis, erosion, cysts, osteophytes, cartilage space loss, malalignment
Ramonda et al. [26]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, cyst, malalignment, erosion
Damman et al. [27]	BML, synovitis, flexor tenosynovitis, osteophytes, joint space narrowing (JSN), cysts
Roux et al. [28]	BML, synovitis, flexor tenosynovitis, osteophytes, JSN, cyst, malalignment, erosion
Liu et al. [29]	BML, synovitis, flexor tenosynovitis, cyst
Kroon et al. [30]	BML, synovitis, osteophytes, JSN, effusion
Kroon et al. [31]	BML, synovitis
Wolski et al. [32]	BML, synovitis, osteophytes, JSN, cyst, malalignment, attrition, erosion, sclerosis

Table 2.
Structural changes in hand osteoarthritis publications reviewed.

A number of questionnaires and clinical examination of the hands were used to assess pain and physical function. Joints were palpated by a rheumatologist to assess the presence of tenderness. To evaluate pain and function in the hands, patients completed self-administered questionnaires including the Australian/Canadian (AUSCAN) hand index, functional index of hand osteoarthritis (FIHOA) and the Arthritis Impact Measurement Scale 2 (AIMS-2). In addition, grip strength was screened for by the use of a hand dynamometer. Linear regression analysis adjusted for age and sex was used to examine the association between MRI abnormalities,

pain questionnaires and grip strength. Logistic regression was used to further validate linear regression analysis by evaluating associations between MRI features and tenderness of the joints. All features were associated with tenderness of the joints, attrition, osteophytes, synovitis and erosions in the PIP and DIP joints respectively. In the multivariate model, BML and synovitis showed a significant association with joint tenderness (both after adjustment for age, sex and radiographic severity) independently of each other. The MRI summed scores were not significantly associated with AUSCAN pain/physical function and the AIMS-2 hand/finger subscales. Conversely, MRI summed scores for osteophytes and attrition were the only MRI-defined features that were associated with grip strength ($B = -0.39$; $p < 0.001$) and FIHOA ($B = 0.58$; $P = 0.005$), respectively.

Studies from the same group have aimed to validate scoring systems for MRI-assessed changes in the hand [20] and demonstrated that MRI-detected changes, including synovitis, BMLs and joint space narrowing are predictors of radiographic progression in hand OA [22]. More recently, the same group have reported that MRI-defined synovitis and BMLs are related to changes in joint tenderness in a 5-year longitudinal study of the Oslo hand osteoarthritis (OA) cohort [19]. A total of 70 participants (63 women, mean (SD) age 67.9 (5.5) years) were included. The investigators evaluated BMLs and contrast-enhanced synovitis in the distal and proximal interphalangeal joints on 0–3 scales in $n = 69$ and 48 patients respectively. The goal was to investigate tenderness of each joint and MRI features in a longitudinal manner. With the use of generalised estimated equations (GEE), the same joints that showed no tenderness at baseline visit were assessed during the follow up visit to determine whether incident/increasing BML and synovitis scores were correlated with de novo tenderness [19]. In joints that showed tenderness during baseline visits, the investigators assessed whether decreasing synovitis and BML were positively correlated with the loss of joint tenderness, adjusting for sex, age, BMI, changes in radiographic OA and follow-up time. The investigators found that the same joints in participants which showed no joint tenderness at their baseline visit were associated with joint tenderness upon increasing/incident BML and synovitis. An increase in incident synovitis was detected in 45 out of 220 joints whereas BML were detected in 47 out of 312 joints.

3.4 Correlation of MRI changes with plain radiography

Several studies have evaluated the reliability of MRI scanning in assessing structural changes in hand OA in relation to clinical symptoms. Korteekas et al. [24] evaluated 16 participants with HOA. The study group had a median age of 57, 62% of the group were women and 13 had erosive OA. In the study, finger joints in the right hand were studied using a 3 Tesla MRI scanner with contrast using gadolinium. Pain was assessed on the same day of MRI examinations and radiographs.

The authors found that detection of synovial thickening for MRI was 43% and for US it was 42%. The most prevalent MRI features were osteophytes, BML and erosions. In contrast to radiographs, MRI scanning was more sensitive at detecting structural changes. A correlation coefficient of 0.43 was found for synovial thickening between US and MRI and it was 0.49 for osteophytes. US was found to be more sensitive for the detection of osteophytes, whereas MRI was more sensitive at detecting synovial thickening. Pain upon palpation was associated with structural changes including synovial thickening, collateral ligaments, BML, erosions and osteophytes.

Other studies have also demonstrated that MRI is a reliable and reproducible method for detecting HOA changes in the interphalangeal joints [23] and thumb base first carpometacarpal joint [30]. Interestingly, in thumb base OA, structural damage was more strongly associated with pain than synovitis [30]. In the HOSTAS

study, which was a large study of 92 participants with HOA [29], interphalangeal and thumb base joints were evaluated to demonstrate that MRI-identified BMLs in HOA were associated with pain and also interacted with synovitis. Findings in DIP/PIP and thumb base HOA have also been replicated in erosive hand OA [26]. With respect to bone texture, roughness in proximal bone texture in finger joints has been shown to be associated with MRI-defined osteophytes in finger joints without radiographic OA, which could assist in detecting early HOA changes.

In a clinical trial of hand OA, Chevalier et al. [33] evaluated French participants in the digital osteoarthritis in refractory hand OA (DORA) study. This multi-centre study recruited 99 participants and randomised 85 to placebo or adalimumab anti-TNF therapy. Mean age was 62 years, 855 were women, with the mean level of pain at baseline of 62 mm by the visual analogue scale (VAS) for pain. The primary outcome measure was the percentage of patients with an improvement of more than 50% in global pain (VAS) between baseline and 6 weeks' therapy. At 6 weeks, there was no significant difference in VAS pain outcomes between the adalimumab and the placebo groups [33]. In a smaller sub-study analysis of the DORA study, Roux et al. [28] evaluated the clinical findings and imaging measures from the DORA study. The group reported that of the 18 participants recruited and 144 joints studied, MRI-measured synovitis in the dominant hand was not correlated with radiological scores, clinical or biological markers of inflammation. A strong correlation was reported between other MRI features including joint space narrowing and osteophyte formation. Serum IL-1 was also associated with structural damage and impaired function.

3.5 Hand OA in the context of inflammatory arthritis

An important issue in hand arthritis studies is the co-existence of OA and rheumatoid arthritis (RA) in many patients. The factor of co-existing OA and RA in people with hand arthritis has recently been addressed by Loef et al. [34]. The group investigated the effect of TNF inhibitors (TNFi) on incidental and progressive hand OA in subjects with recent-onset RA over a 10 year follow-up. Plain radiographs of 262 subjects with RA (mean age 52 years, 66% women), from the BeSt study had osteophyte scoring conducted. Osteophytes in the DIP/PIP joints were scored using the Osteoarthritis Research Society International atlas (0–3; summed score 0–54) and according to Kellgren-Lawrence (KL) score (0–4; summed score 0–72) at baseline and 10 year follow-up. The use of TNF inhibitor treatment was assessed at 3 monthly visits. The group evaluated associations between TNF inhibitor treatment and HOA using generalised linear regression models and estimating equations. A total of 58% of patients were treated with TNFi with a median duration of 42 months. There were 55% of patients who had hand OA in any IP joint at baseline. For individual patients, TNFi duration did not affect incidental hand OA. However, on a monthly basis, TNFi treatment resulted in a reduced relative risk (RR) of hand OA progression in the DIP joints (relative risk (RR) 0.987 (95% CI 0.978, 0.996) but not in the PIP joints. The study concluded that TNFi treatment was associated with a reduced risk of hand OA progression in DIP joints but not in PIP joints after 10 years. The effect sizes in this study were small and were limited to DIP joint involvement, but suggest that TNF alpha can influence disease course in HOA.

4. Discussion

This systematic review has identified studies from the literature which demonstrate that joint space narrowing, osteophytes, synovitis and BMLs are all structural

changes in HOA that are associated with significant symptomatic burden of pain and functional impairment. MRI and US have been shown to be effective imaging modalities that detect more structural changes than plain radiography alone. MRI allows examination of the joint as a whole organ to directly visualise intra-articular structures significant to the progression of OA such as BMLs, synovitis, osteophytes and erosions in relation to radiographic changes and pain. Our systematic review has also found that synovitis and BMLs in HOA which are detectable by MRI and US in particular, are associated with progression in symptoms over time and therefore may represent valid targets for future interventions aimed at modifying these structural changes. Joint space narrowing and osteophyte formation were also identified to have good correlation between plain radiography and MRI/US identified changes. Future novel therapeutics would benefit from correlation with changes in synovitis, BMLs and joint space narrowing in relation to pain and functional outcome for HOA.

Our systematic review has found that a number of different cohorts around the world demonstrate structural changes observed in HOA. However, the majority of the studies were in European populations. Future studies in distinct ethnic groups around the world would be helpful to compare and contrast data from existing published studies.

Since HOA has a higher prevalence in females, as reflected by the preponderance of women participants in the studies we identified, future studies which report changes in male participants with HOA, with data on occupation, since manual occupations are known to have a higher risk of HOA, are to be welcomed to compare and contrast the changes observed.

Emerging data from the articles we have reviewed suggest that people with HOA could potentially be stratified for imaging-based structural changes e.g. subjects showing inflammatory changes as evidenced by US or MRI-defined synovitis that could be targeted by NSAIDs or intra-articular steroid injections, or a predominant bone-cartilage damage profile, evidenced by the presence of MRI-defined cartilage loss, joint space narrowing and bone oedema that could be targeted using novel therapeutic agents. Imaging modalities such as MRI and/or US that demonstrate additional structural changes not visualised by plain radiography could aid in improved stratification and development of novel therapeutics for HOA in the future.

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