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Osteoarthritis and Cartilage

Review

Synovitis and bone marrow lesions associate with symptoms and radiographic progression in hand osteoarthritis: a systematic review and meta-analysis of observational studies

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SUMMARY

Aims: To systematically review observational studies for the association between features detected on ultrasound (US) and magnetic resonance imaging (MRI) and, symptoms, signs and radiographic progression of hand osteoarthritis (OA).

Methods: Medline, Web of Science, EMBASE, CINAHL and AMED were searched from inception to 14th January 2020 to identify relevant studies. Quality of studies was assessed using the Newcastle–Ottawa scales and data were extracted. Odds ratios (OR) and linear regression coefficients and 95% confidence intervals (CI) were pooled using the random-effects model (METAN package, Stata v16.1). Heterogeneity and publication bias were assessed.

Results: Thirty-two studies using US and MRI comprising 1,350 and 638 participants respectively were included. While only grey-scale synovitis (GSS) associated with AUSCAN-pain (pooled Regression coefficient (95% CI): 0.46 (0.13–0.79); 0–20 scale for AUSCAN-pain), US-detected osteophytes, GSS and power Doppler (PD) [pooled ORs (95% CI): 2.68(2.16–3.33), 2.38(1.74–3.26) and 2.04 (1.45–2.88)] as well as MRI-detected bone marrow lesions (BMLs), synovitis, osteophytes, and central bone erosions (CBEs) associated with joint tenderness [pooled ORs (95% CI): 2.59(2.12–3.18), 2.17(1.85–2.54), 2.15(1.55–2.99), and 2.41 (1.45–4.02)] respectively. US-detected GSS and PD associated with radiographic progression of CBEs [pooled ORs 5.37, 5.08], osteophytes [pooled ORs 5.17, 6.45], and joint space narrowing (pooled ORs 4.28, 4.36) whilst MRI-detected synovitis and BMLs associated with increasing KL grades with pooled ORs 2.92, 2.54 respectively.

Conclusions: US and MRI-detected structural and inflammatory changes associate with tenderness, whilst articular inflammation and subchondral bone damage associate with radiographic hand OA progression. There was inconsistent relationship between these changes and pain.

Introduction

Osteoarthritis (OA) is the commonest form of arthritis to affect synovial joints[1] including joints in the hands[2,3]. The prevalence of symptomatic hand OA ranges between 13% and 41% in adults[4–6], and increases with age. People with hand OA often experience pain, stiffness, functional impairment, and reduced quality of life[7–9], especially those with thumb-base OA or when there is severe damage to the interphalangeal (IP) joints[10,11]. However, the relationship between structural and inflammatory changes in the affected hand joints, and symptoms and disease progression is poorly understood.

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A number of relatively small cross-sectional and cohort studies have examined ultrasound (US) and magnetic resonance imaging (MRI) features as biomarkers of hand symptoms[12–15], and as determinants of hand OA progression[16,17]. Varying findings have been reported in these studies, and a systematic review examining the association between these findings, and symptoms, signs, and disease progression has not been performed. It is important to systematically review the literature in order to provide a better understanding of the contribution of structural (e.g., osteophyte, joint space narrowing), subchondral bone (e.g., bone marrow lesion (BML)) and inflammatory (e.g., synovitis) changes to symptoms of hand OA, and to identify patients at high risk of disease progression so that they may be managed adequately with therapy input, analgesia, or intra-articular corticosteroid injections. Improved understanding of these factors will also facilitate their prioritisation as stratification factors and/or inclusion criteria in hand OA clinical trials.

Synovitis is implicated as a cause of pain in OA[18] and associates with disease progression[19]. At the knee, the most often studied site in OA, both US and MRI detected synovial changes, and MRI detected bone marrow lesions (BMLs) associate with pain[20,21], while MRI-detected synovitis associates with increased risk of progression of OA[22]. On the contrary, other features such as osteophytes and cartilage loss assessed using MRI have not been associated with pain in knee OA[23,24]. Thus, we hypothesized that some features of hand OA such as synovitis, and subchondral bone marrow changes will associate with symptoms, and disease progression. The purpose of this study was to systematically review observational studies investigating the association between features of OA detected on US or MRI and, symptoms, signs and radiographic progression in people with hand OA.

Methods

A systematic review protocol was developed and registered in PROSPERO (CRD42018095677).

Literature search

The systematic literature search was performed in Ovid Medline, Embase, CINAHL, AMED and Web of Science databases from inception until April 2018 and updated on 14th January 2020. The search aimed to retrieve all manuscripts utilising US or MRI studies that investigated hand OA. The search included three domains: (a) hand OA, (b) US and MRI features, and (c) symptoms and signs. Keywords were “hand”, “osteoarthritis” “synovial effusion”, “synovial hypertrophy”, “grey-scale synovitis” (GSS), “power Doppler” (PD), “bone marrow lesions” (BMLs), “osteophytes” “joint space narrowing” (JSN), “central bone erosions” (CBEs) and “symptoms”, their synonyms and closely related words. See Supplementary Table S1 for details of the search strategy. Reference lists of relevant retrieved articles were checked manually to identify any relevant publications not captured by the main search, and retrieved titles and abstracts were managed in Endnote X8.0.1 (Bld. 10,444).

Inclusion and exclusion criteria

Studies were selected if they were observational studies, i.e., case–control, cross-sectional, and prospective or retrospective cohort studies, recruiting adults (age > 18 years) with hand OA, and investigating association between features detected on US or MRI and (1) symptoms/signs, or (2) radiographic progression of hand OA. Data from case–control and cross-sectional studies were used to examine association between changes detected on US or MRI and clinical features of hand OA, whereas data from cohort studies were used to assess the association between changes detected on US or MRI and radiographic progression. Studies investigating other forms of arthritis, e.g., rheumatoid arthritis or psoriatic arthritis, and non-human studies were excluded. Conference abstracts were excluded as they contain insufficient data for a systematic review. Randomised controlled trials (RCTs) were also excluded as the natural history of the disease has been changed by intervention and they are restricted by rigid inclusion and exclusion criteria. No language restrictions were applied in the search.

Data extraction and outcome measures

Data extraction was performed using a customised form specifically developed for this review. Information extracted included publication year, country, source of funding, population characteristics (mean age, % female, mean body mass index (BMI)), diagnostic criteria used, study design, imaging modalities used, joints assessed, and measures of effect such as odds ratio (OR), risk ratios (RR), correlation coefficient (r), linear regression coefficient (R) and 95% confidence intervals (CI) between features detectable on US or MRI and clinical, and radiographic outcomes. US and MRI features of interest included osteophytes, CBEs, JSN, effusion, synovitis, power Doppler (PD) and BMLs. Clinical outcomes examined were:

(a) symptoms: participant-reported hand pain, functional impairment and stiffness measured using any relevant hand OA outcome measure including but not limited to the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), Visual-Analogue-Scale (VAS) and functional index for hand OA (FIHOA), and
(b) investigator-assessed physical sign: joint tenderness (pain on palpation).

Where a study utilised multiple hand OA outcome measures, data from only AUSCAN, VAS and functional index for hand OA (FIHOA) were included in the analysis. Radiographic outcomes investigated were incidence (for unaffected joints at baseline) or progression (for joints with less severe abnormality at baseline) of osteophytes, JSN, CBEs, and worsening Kellgren Lawrence (KL) grade at follow-up. Where multiple publications utilised data from the same set of participants and reported the same outcome measures, the publication with the largest sample size was included in the review. However, if different outcomes were reported from the same cohort in different manuscripts all such publications were included in the review to maximise the available data.

Quality assessment

The Newcastle–Ottawa scale (NOS) for case–control and cohort studies[25] and a modified NOS for cross-sectional studies[26] were used. These assessments take account of selection bias, comparability based on analysis, and outcome reporting. The modified NOS for cross-sectional studies additionally also includes justification of sample size as part of quality assessment[26]. Assessing quality based on sample size is reasonable since small studies tend to over-estimate effect size that may be used as a surrogate of poor quality[27]. The quality assessment uses the star system, ranging from 0 to 9 stars for case–control and cohort studies, and 0–10 stars for cross-sectional studies. A higher number of stars represents better quality.

Validation of review steps

The screening of titles, abstracts and full-texts, data extraction, and risk of bias assessment were performed by one reviewer (AO). Three second reviewers (JK, SS, and KY), already trained in systematic review methods, independently repeated each step on a randomly selected sample for validation. JK screened titles and abstracts of 100 randomly selected citations. SS screened full text and assessed risk of bias on a randomly selected 10% ($n = 18$) and 20% ($n = 6$) of eligible articles respectively, while KY extracted data of a randomly selected 10% ($n = 6$) of eligible articles. Discrepancies were discussed and resolved with an experienced reviewer (AA).

Statistical analysis

Data analysis was performed using StataSE version 16.1, where Rs (95% CI) for cross-sectional association between features detected on US and MRI and symptoms were pooled using random-effects model with restricted maximum-likelihood (REML) method in the METAN package. ORs (95% CIs) for association between features detected on US and MRI and, signs and radiographic progression were separately pooled using the METAN package (please see APPENDIX A and Supplementary Methods in Supplementary file for details). Heterogeneity was assessed using the I^2 test. This was interpreted according to the Cochrane reviews classification (0–40% - might not be important; 30–60% - may represent moderate heterogeneity; 50–90% - may represent substantial heterogeneity; 75–100% - considerable heterogeneity)[28]. Publication bias was assessed using the Egger's test. The 95% CI and *p*-values were used for statistical significance.

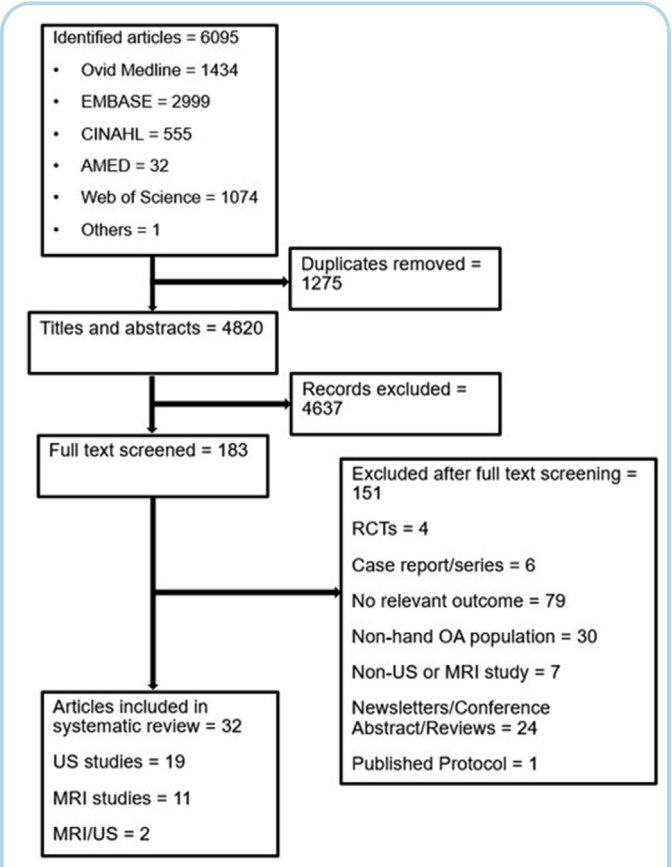

Fig. 1 Literature search and screening flow diagram. AMED- Allied and Complementary Medicine Database; CINAHL- Cumulative Index to Nursing and Allied Health Literature; MRI- Magnetic Resonance Imaging; OA-Osteoarthritis; RCTs- Randomized Controlled Trials; US-Ultrasonography.

Results

Study selection

The database searches identified 6,095 citations. After deduplication and screening of titles and abstracts, 183 citations were selected for full-text screening. Of these, 32 met the inclusion criteria, including 19 using only US (13 association and seven progression), 11 using only MRI (7 association and four progression) and two using both US and MRI (1 association and one progression) (Fig. 1). Agreement between AO and JK, SS and KY for screening/extraction procedures and risk of bias assessment were all excellent at 96%, 100% and 94%, and 97%, respectively.

Study characteristics

The 32 studies were conducted in eight countries: the Netherlands[13,17,29–38], Norway[14,39–46], United Kingdom[12,47,48], France[49,50], Italy[16,51], Australia[15,52], Greece[53], and Brazil[54]. They included 13 cohort, 3 case–control, and 16 cross-sectional studies, and the vast majority of studies (30 of 32 studies) recruited participants from specialist hospital clinics. Their combined sample size was 1,350 (72% women) and 638 (87% women) participants for US and MRI studies, respectively. The mean age and BMI of participants included in the US and MRI studies was 65.5 years and 27.2 kg/m^2, and 61.5 years and 26.3 kg/m^2, respectively. All MRI studies recruited from hospital clinics, whereas two studies that investigated US in hand OA recruited from the community ($n = 612$, 54% women)[15,52]. The mean age and BMI of participants recruited from community setting in these two US studies was higher than those recruited in US studies from hospital clinics (71.3 years vs 60.7 years, and 28.2 kg/m^2 vs 26.0 kg/m^2). A description of the included studies is reported in Supplementary Table S2.

Quality assessment

The median quality scores were 8 (0–9 scale) for cohort, 6 (0–9 scale) for case–control and 7 (0–10 scale) for cross-sectional studies (Supplementary Table S3(A)–(C)).

In addition to this, there was considerable heterogeneity in the way data was categorised and analysed in the included studies (Supplementary Table S2). For instance, US and MRI features were described either dichotomously (present or absent) or as sum of scores (summation of grades of each pathology from all joints imaged), joint count (number of joints affected) or quantitatively in terms of thickness or length of the abnormality detected. This limited pooling of the data.

Association between features detected on US or MRI and clinical outcomes

The association was investigated in 20 studies: 13 using US[12,13,15,29,33,45–49,52–54], seven using MRI[14,34,36–38,50,51] and one using both US and MRI[35]. Summated grades of grey-scale synovitis

Imaging features	AUSCAN pain	VAS pain	AUSCAN function	AUSCAN stiffness
No. of affected joints	Pooled odds ratio (95% CI) [I^2 in %]			
Grey-scale synovitis	1.16 (0.81, 1.66) [0.0]	1.27 (0.91, 1.78) [0.0]	1.29 (0.97, 1.72) [0.0]	1.34 (0.99, 1.83) [0.0]
Power Doppler	1.27 (0.95, 1.69) [0.0]	0.73 (0.16, 3.23) [83.1]	1.35 (0.99, 1.84) [0.0]	1.40 (1.03, 1.91) [0.0]
Osteophytes	0.90 (0.41, 2.02) [57.7]	1.29 (0.95, 1.76) [0.0]	1.21 (0.89, 1.64) [0.0]	1.33 (0.98, 1.82) [0.0]
Summated grades	Pooled linear regression coefficient (95% CI) [I^2 in %]			
Grey-scale synovitis	0.46 (0.13, 0.79)* [0.0]	0.35 (−1.41, 2.10)** [0.0]	0.31 (−0.28, 0.89)*** [0.0]	–
Power Doppler	0.10 (−0.85, 1.05)* [34.39]	4.87 (−6.20, 15.95)** [81.4]	0.39 (−0.88, 1.67)*** [21.11]	–
Osteophytes	–	−0.20 (−0.74, 0.35)** [0.0]	–	–

AUSCAN-Australian/Canadian Hand Osteoarthritis Index, VAS-Visual Analogue Scale, *-(0–20 scale), **-(0–100 mm scale), ***-(0–36 scale). Two studies ($n = 554$) were used to derive pooled odds ratio while three studies ($n = 438$) were used to derive the pooled regression coefficient.

Table I Pooled effect sizes for the cross-sectional association between ultrasound features and symptoms

Osteoarthritis and Cartilage

(GSS) associated with AUSCAN-measured pain [pooled R (95% CI) 0.46 (0.13–0.79); 0–20 AUSCAN-pain scale][13,46] but not with VAS pain [0.35 (−1.14, 2.10); 0–100 mm scale][13,15]. Similarly, the number of joints with PD associated with AUSCAN stiffness (pooled Odds ratios (OR) (95% CI) 1.40 (1.03–1.91)) but not with AUSCAN pain [1.27 (0.95, 1.69)], VAS [0.73 (0.16, 3.23)] or AUSCAN physical function [1.35 (0.99, 1.84)][12, 52]. Further analysis using the number of joints with osteophytes showed no association with symptoms (Table I). Heterogeneity between studies involved in these analyses was unimportant except for the meta-analyses between PD and VAS pain, for which there was considerable heterogeneity, and between osteophyte and AUSCAN pain, for which there was moderate heterogeneity (Table I).

Six MRI studies investigated symptoms[14,36–38,50,51]. Of these, three found no associations[36,37,50]. However, associations were observed between FIHOA and synovitis, osteophytes, and JSN in one study ($n = 85$)[14], and in other studies VAS-measured pain associated with synovitis, osteophytes[38], and CBEs[51]. Data could not be meta-analysed because estimates of association were not reported and results were narratively described in the majority of studies (Supplementary Table S4(A) and (B)).

Several US and MRI features associated with joint tenderness, the pooled ORs (95% CI) derived from five US studies[33,35,46,48,49] being 2.68 (2.16–3.33) for osteophytes, 2.38 (1.74–3.26) for GSS and 2.04 (1.45–2.88) for PD. Similar results were observed for MRI features from five studies[14,34,36,37,51], with pooled ORs (95% CI) of 2.59 (2.12–3.18) for BMLs, 2.17 (1.85–2.54) for synovitis, 2.15 (1.55–2.99) for osteophytes, and 2.41 (1.45–4.02) for central bone erosions (CBEs). However, no association was observed between joint tenderness and US-detected effusion (1.76 (0.78, 3.99)) or MRI-detected JSN (1.99 (0.69, 5.74)) (Table II). Heterogeneity between studies was substantially high for US effusion, GSS, and PD, moderate for MRI JSN and CBEs and, unimportant for US osteophytes and MRI BMLs, synovitis and osteophytes (Table II). The funnel plots for visual assessment of publication bias were slightly asymmetric particularly for US features (Supplementary Fig. S1).

	Number of studies	Study size	Pooled odds ratio (95% CI)	I^2% (P_{heter})	Publication bias
Ultrasound features					
Osteophytes	2	117	2.68 (2.16–3.33)	0.0 (0.906)	–
Effusion	3	197	1.76 (0.78–3.99)	81.1 (0.005)	0.374
Grey-scale synovitis	3	432	2.38 (1.74–3.26)	71.1 (0.031)	0.088
*Grey-scale synovitis	2	377	2.03 (0.68–6.08)	84.5 (0.011)	–
Power Doppler	4	487	2.04 (1.45–2.88)	62.6 (0.045)	0.006
*Power Doppler	2	377	2.07 (0.70–6.16)	84.0 (0.012)	–
MRI features in DIP and PIP joints					
Osteophytes	2	141	2.15 (1.55–2.99)	0.0 (0.760)	–
Joint space narrowing	2	141	1.99 (0.69–5.74)	40.3 (0.196)	–
Central bone erosions	3	152	2.41 (1.45–4.02)	46.6 (0.154)	0.058
†Bone marrow lesions	5	781	2.59 (2.12–3.18)	0.0 (0.763)	0.222
†Synovitis	5	781	2.17 (1.85–2.54)	0.0 (0.727)	0.376

* Analysis included pathologies present in thumb-base only.
† Analysis included pathologies present in both thumb-base and interphalangeal joints, CI-confidence interval, (P_{heter})-p value for heterogeneity, DIP-distal interphalangeal, PIP-proximal interphalangeal, MRI- Magnetic Resonance Imaging.

Table II Cross-sectional association between ultrasound/MRI features of hand osteoarthritis and joint tenderness

Osteoarthritis and Cartilage

However, small study effect was only confirmed for PD (Table II). See Supplementary Table S5(A) and (B) for findings from individual studies for joint tenderness.

Excluding data for studies that did not report separate findings for the first carpometacarpal (CMC) joints, we observed that GSS and PD in the first CMCJ did not associate with joint tenderness [pooled ORs 95% CI: 2.03 (0.68, 6.08) and 2.07 (0.70, 6.16), respectively][35,46]. It was not possible to perform this analysis for other US features because most studies presented composite results for interphalangeal (IP), metacarpophalangeal (MCP), and first CMC joints ($n = 7$)[12, 13, 29, 33, 48, 52, 53], while others assessed only IPJs ($n = 3$)[45, 49, 54] and thumb-base ($n = 3$)[15, 35, 47]. One study assessed IP and first CMC joints and presented separate results[46].

US and MRI features and progression of radiographic changes

This was examined in 13 studies including eight using US[16,17,29–31,39,40,47], four using MRI[32,42–44], and one using both imaging modalities[41]. One US study was excluded due to intra-articular injection offered to all participants between baseline and follow-up visits[47]. The pooled ORs (95% CI) for association between GSS and progression of osteophytes, JSN, and CBE change was [pooled OR (95% CI)]: 5.17 (3.24–8.25), 4.28 (3.29–5.57), and 5.37 (3.12–9.26) respectively (4 studies, $n = 159$)[16,17,31,39]. Finally, PD associated with progression of osteophytes, JSN, and CBEs with the pooled ORs (95% CI) of 6.45 (3.20–12.97), 4.36 (2.94–6.48), and 5.08 (3.14–8.20), respectively (4 studies, $n = 159$)[16,17,30,39] (Fig. 2). Similar results were observed between MRI features and progression of KL grade, the ORs (95% CI) pooled from two studies ($n = 161$) being 2.92 (2.01–4.25) for synovitis and 2.54 (1.72–3.76) for BMLs[32,44] (Fig. 3). Heterogeneity between studies was not substantial for all analyses except for association between GSS/PD and progression of osteophytes. There was no evidence for publication bias (Supplementary Fig. S2).

Furthermore, baseline PD independently associated with the development of new radiographic CBEs (pooled OR (95% CI): 4.25 (2.25–8.04), whereas no association was demonstrated for effusion and GSS, the OR (95% CI)) pooled from two studies being 2.18 (0.64–7.40) and 3.14 (0.49, 20.17), respectively ($n = 81$)[16,30] (Fig. 4). Further analyses were performed based on the severity of US and MRI features at baseline. A dose-dependent relationship was

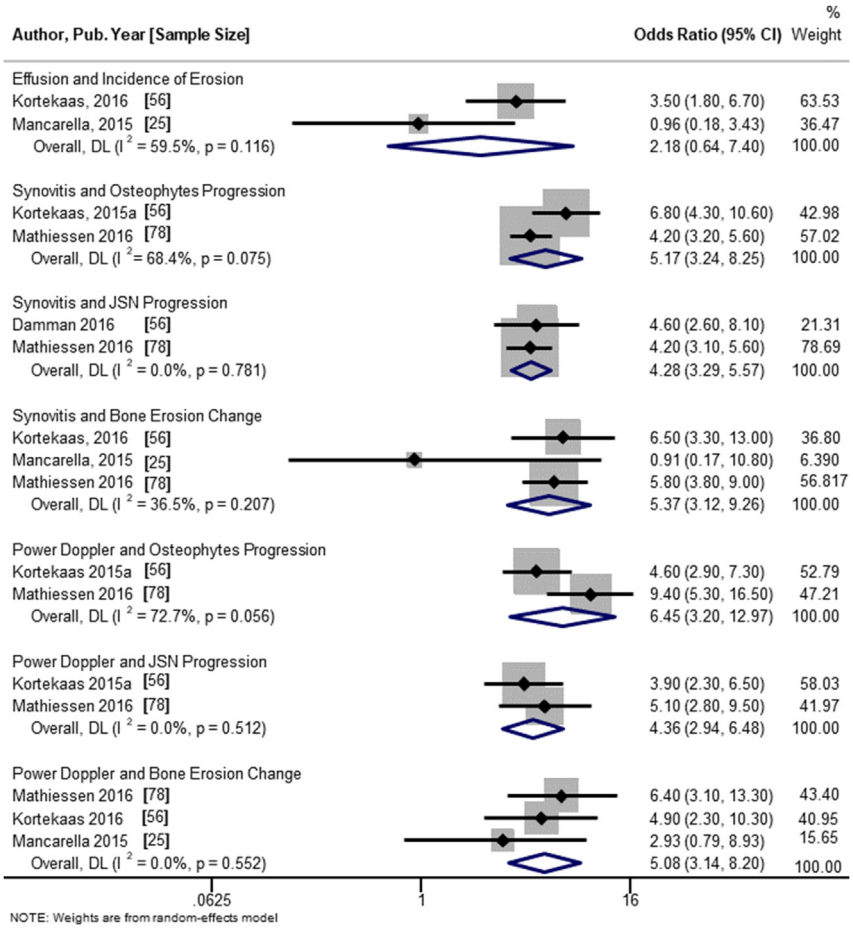

Fig. 2 Forest plot of odds ratio between ultrasound features and incidence or progression of radiographic changes in hand osteoarthritis. For radiographic bone erosion change as outcome, both incidence and progression were pooled together in this analysis. The unfilled diamond in the forest plot indicates the pooled odds ratio and the corresponding confidence intervals (CI) for each imaging feature. JSN-joint space narrowing, Pub. Year-publication year.

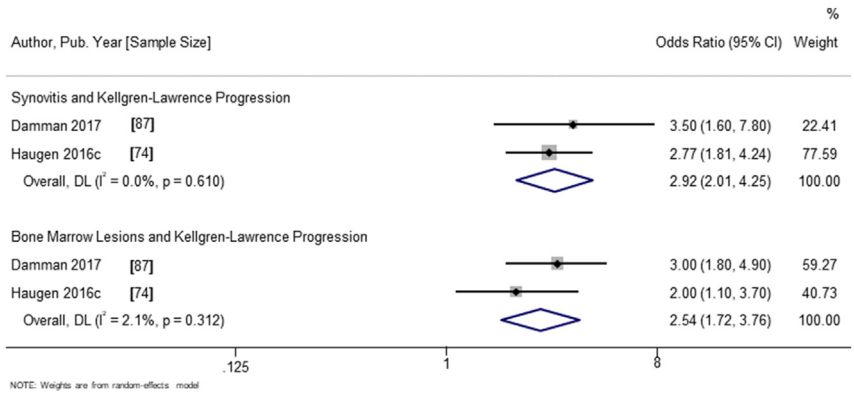

Fig. 3 Forest plot of the association between magnetic resonance imaging features and progression of radiographic changes in hand osteoarthritis. The unfilled diamond in the forest plot indicates the pooled odds ratio and the corresponding confidence intervals (CI) for each imaging feature. Pub-publication.

observed between presence of GSS, PD and MRI synovitis at baseline, and progression of radiographic osteophytes, JSN, and KL grade (Table III).

Two studies reported the association between US and MRI-detected structural features and radiographic hand OA progression in the same set of participants. One investigated US detected osteophytes and found associations with incident radiographic osteophytes, JSN and KL grade[40] while the other investigated MRI osteophytes, JSN and CBEs and found association with incident radiographic CBEs[44] (See details Supplementary Table S6(A) and (B)).

Discussion

This is the first systematic review to examine the association between US and MRI-detected changes and (a) clinical features, and (b) radiographic progression in people with hand OA. The key findings are: [1] inconsistent evidence for association between features of joint inflammation (detected on either US or MRI) and symptoms of hand OA; [2] consistent evidence that joints with US or MRI-detected inflammatory or structural features are 2–3 times more likely to be tender than unaffected joints in hand OA; and [3] consistent evidence that joints with US or MRI-detected inflammatory features and MRI BMLs, are 2–6 times more likely to either develop a new radiographic abnormality or to show worsening of pre-existing radiographic change, with a dose response relationship.

US-detected osteophyte, GSS and PD signal as well as MRI-detected osteophyte, CBE, BMLs and synovitis were consistently associated with joint tenderness in hand OA. Although, the associations with symptoms appeared to be inconsistent, our pooled results suggest that inflammatory features such as GSS and PD associate with symptoms of hand OA. For instance, we observed that a unit increase in the sum score of GSS (minimum value 0,

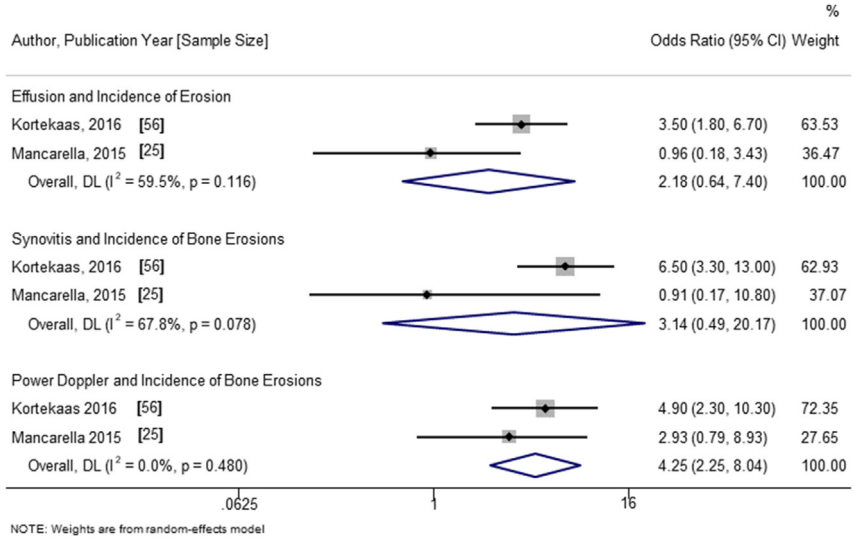

Fig. 4 Association between ultrasound features and incident bone erosion.

Baseline Imaging features	Follow-up outcomes	Pooled Odds Ratio (95% CI) [I^2 in %]			
Grey-scale Synovitis grades*		0	1	2	3
	Osteophytes progression	1	3.89 (1.69–8.96) [83.8]	7.33 (5.32–10.09)† [0.0]	–
	JSN progression	1	3.78 (2.74–5.23) [0.0]	3.91 (2.61–5.86) [0.0]	11.51 (5.71–23.18) [0.0]
Power Doppler grades*		0	1	2	3
	Osteophytes progression	1	4.35 (1.87–10.16) [69.7]	15.09 (8.24–27.63)† [0.0]	–
	JSN progression	1	3.27 (2.02–5.31) [0.0]	8.05 (4.29–15.13)† [0.0]	–
MRI Synovitis grades$		0	1	2	3
	KLG progression	1	2.00 (1.32–3.03) [0.0]	5.01 (1.81–13.88)† [72.2]	–

* [2 studies, $n = 134$, $I^2 =$]; $[2 studies, $n = 130$, $I^2 =$].
† [cut-off ≥ grade 2]; CI-confidence interval.

Table III Dose–response analysis for association between features detected on US and MRI and progression of radiographic changes

Osteoarthritis and Cartilage

maximum value 30–90 depending on the number of joints examined) is accompanied by an increase of 0.5 in the 20-point AUSCAN pain score. Thus a modest 4-point increase in summated GSS score will result in clinically significant change in AUSCAN pain score[55]. Similarly, the number of joints with PD associated with AUSCAN stiffness, while there was inconsistent evidence for its association with hand pain and function assessed using AUSCAN. Exploring relationships across individual studies, we observed that presence of PD signal associated with hand pain assessed using VAS in community-based studies[15,52], but not in hospital-based studies[12,13,53]. Statistical pooling was not possible across these studies due to different ways in which the data were categorised and analysed. It is likely that hospital-based studies recruit patients with advanced hand OA where the additional presence of inflammation has a smaller impact on symptoms than in community-based studies that will typically include patients with milder disease. Thus, further community-based studies are needed in the field.

We did not observe an association between osteophytes and hand OA clinical outcomes. The discordance between symptoms and structural changes in OA is well recognised[56]. This may be due to the fact that the long-term outcome of IP joint OA is often good. Such discordance and overall good patient-centred outcome may be explained by the perspective of OA as the inherent repair process of synovial joints, which often can compensate for adverse insults but which leaves the joint anatomically altered, possibly resulting in tenderness, but not contributing to long-term pain or disability[57]. In addition, the perception of symptoms such as pain is confounded by several central and peripheral factors other than structural change[58].

We observed that hand joints with inflammation detected on US or MRI were at higher risk of developing a new radiographic feature or worsening of a pre-existing feature in a dose-dependent manner. The incidence and progression of structural OA changes may have different pathophysiology and risk factors[32,59]. We were unable to separate these two outcomes because researchers have used “either incidence or progression of radiographic change” as a composite outcome. However, this differentiation was possible for incident radiographic CBEs. PD associated with incident radiographic erosions, and although the 95% CI around the pooled ORs for association with effusion and GSS suggest considerable uncertainty, the point estimates remain clinically important (Fig. 4). This difference may be due to the fact PD depicts active inflammation[60] whereas effusion may result from reduced lymphatic capacity in OA[61], and effusion and GSS may represent either inactive or low-grade inflammation, respectively, and further studies in this area are needed. This suggests that inflammation may precede radiographically-detectable structural changes in hand OA and plays a key role not only in the progression but also in the initiation of structural changes in hand OA. This may explain the high burden of inflammation in erosive compared to non-erosive hand OA[41,62–64].

Our observation also raises the question as to whether treatment of inflammation could reduce structural progression in hand OA. In one RCT, where people with hand OA were randomised to either 40 mg of subcutaneous adalimumab or placebo, no difference in radiographic progression was observed between the two groups[65]. However, this study recruited only people with erosive hand OA, an aggressive hand OA phenotype, and the follow-up time (12 months) may have been too short to detect significant differences in radiographic progression. A recent meta-analysis of RCTs examined the effectiveness of treating inflammation in knee or hand OA and reported no significant difference between disease-modifying anti-rheumatic drugs commonly used to treat autoimmune rheumatic diseases and placebo[66]. However, the drugs included in this review may not reduce inflammation in OA, and the outcome of interest was analgesia, and multiple central factors (e.g., catastrophizing)[58] as well as peripheral factors (e.g., joint damage) influence pain experience.

Aside from inflammatory features, MRI detected BMLs also associated with progression of structural change, which suggests that subchondral bone plays a key role in hand OA progression. This is consistent with findings at the knee[67]. We also observed that US detected osteophytes associate with incident radiographic JSN, osteophytes, and worsening KL grade[40], while MRI detected osteophytes, CBEs and JSN associate with incident radiographic CBEs[44]. This supports the viewpoint that OA is a whole joint condition and that all articular tissues are involved in its pathogenesis[18]. Although these changes may occur together in different tissues of the joint from the onset, structural changes may take longer to become apparent on imaging, however, once they become apparent, further radiographic progression is likely. Furthermore, the concordance between US/MRI detected structural changes and incident radiographic changes after a few years may also result from the high sensitivity of US and MRI in detecting structural changes that are not yet visible on plain radiographs[68,69]. Therefore, further studies are required to examine structural changes of hand OA using US or MRI and to follow-up on the changes over time

using the same imaging modality. Although our findings may suggest that both synovial inflammation and subchondral bone changes are important in the course of structural changes in hand OA, further studies are required to better understand the mechanism by which inflammation and increased subchondral bone turnover occurs and contributes to progression of hand OA. This will allow the development of strategies to minimise joint damage in hand OA.

There are many limitations to this review. Firstly, there were substantial differences in joints assessed, outcome measures used, and the way in which data were categorised for analysis across the included studies. As a result, only data for 2–5 studies could be included in the meta-analyses. Secondly, there was significant heterogeneity in the association between US detected PD and VAS pain, and between US detected inflammatory features and joint tenderness and progression of osteophytes. This is not unexpected since US is a highly operator-dependent imaging modality. However, there was very low or no heterogeneity in MRI studies. As the findings from MRI studies were consistent with those from US studies they provide confidence in our findings. Additionally, publication bias was observed in the analyses between PD and joint tenderness. This could result from the fact that PD is present in relatively few joints in hand OA and it is possible for authors to not report exposures and outcomes for which there are no associations. Moreover, we were not able to provide separate estimates for IP joint and thumb-base OA with the notable exception of association between GSS/PD and tenderness, of which no association was found for thumb-base tenderness. Thumb-base OA is a separate hand OA phenotype from IP joint OA and we tried to explore any differences in association for all outcomes in this review. However, due to summation of imaging findings across different joint groups, and only a few ($n = 4$) studies provided separate results for 1st CMCJ OA, we were unable to perform most subgroup analysis for hand OA subtypes. Finally, most included studies recruited consecutive patients attending hospital clinics, and only two studies recruited community dwelling adults. This limits the generalisability of our finding as the majority of the participants in the included studies could have more severe or atypical OA, requiring referral to secondary care.

In conclusion, US and MRI-detected inflammatory and structural changes associate with joint tenderness whilst the association with symptoms appears to be inconsistent. Articular inflammation and subchondral bone changes associate with development and progression of structural OA changes. This suggests that both changes may precede structural changes and may be used to identify a subset of hand OA patients at risk of adverse outcome. Finally, given the substantial methodological differences in the included studies, there is a need for hand OA researchers to agree on the joints to be included, the minimum set of outcome measures to be used, the optimal strategy for combining imaging findings (i.e., sum scores, number of joints affected), and reporting standards for use in all future imaging studies. This will greatly improve comparability across studies and facilitate future evidence synthesis endeavours.

Contributors

Study concept and design: AA, WZ, MD, and AO. The first reviewer (AO) did the literature search, screened titles/abstracts and full-text, extracted data, assessed study quality, and performed the analysis. JK performed validation on titles/abstracts screening, SS validated full-text screening and quality assessment, KY validated data extraction. Discrepancies were resolved with AA. AO wrote the first draft, which was reviewed by AA, WZ, and MD. The final version for publication was approved by all the authors.

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Conflict of interest

None to declare.

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Supplementary data

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