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Chapter 2

Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review

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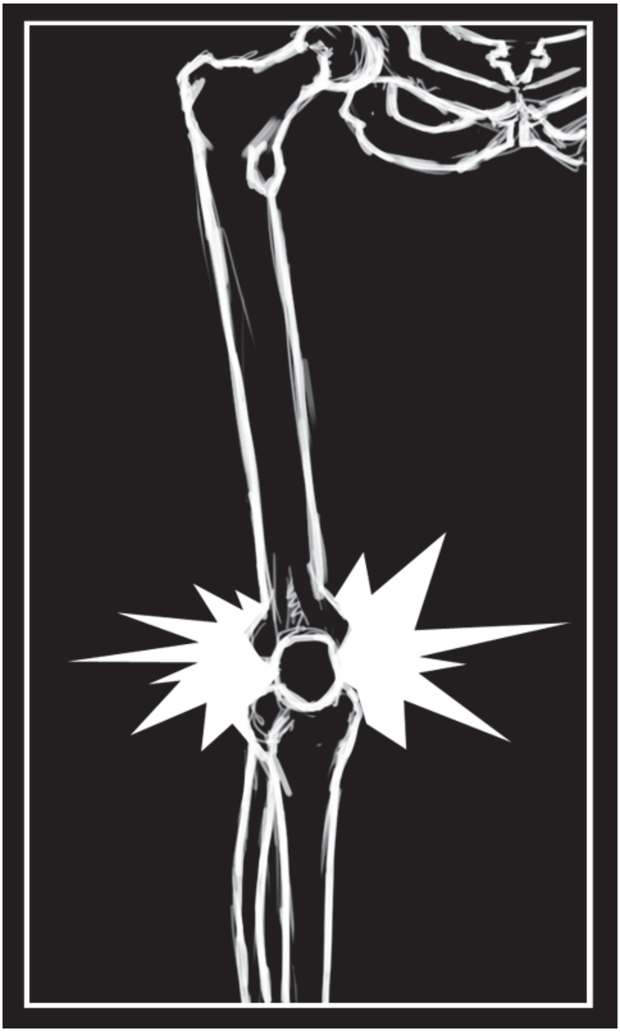

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ABSTRACT

Objective

To systematically evaluate the association between MRI findings (cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition) and pain in patients with knee osteoarthritis (OA) in order to establish the relevance of such findings when assessing an individual patient.

Methods

The Medline, Web of Science, Embase and Cumulative Index to Nursing & Allied Health Literature (CINAHL) databases up to March 2010 were searched without language restriction to find publications with data on the association between MRI findings of knee OA (exposure of interest) and knee pain (outcome). The quality of included papers was scored using a predefined criteria set. The levels of evidence were determined qualitatively using best evidence synthesis (based on guidelines on systematic review from the Cochrane Collaboration Back Review Group). Five levels of evidence were used: strong, moderate, limited, conflicting and no evidence.

Results

A total of 22 papers were included; 5 had longitudinal and 17 cross-sectional data. In all, 13 reported a single MRI finding and 9 multiple MRI findings. Moderate levels of evidence were found for BML and effusion/synovitis. The odds ratio (OR) for BML ranged from 2.0 (no CI was given) to 5.0 (2.4 to 10.5). The OR of having pain when effusion/synovitis was present ranged between 3.2 (1.04 to 5.3) and 10.0 (1.1 to 149). The level of evidences between other MRI findings and pain were limited or conflicting.

Conclusions

Knee pain in OA is associated with BML and effusion/synovitis suggesting that these features may indicate the origin of pain in knee OA. However, due to the moderate level of evidence these features need to be explored further.

2.1. INTRODUCTION

Knee is the major site of osteoarthritis (OA), the most common rheumatic disorder which is characterized by pain that leads to significant restriction in patients' daily activity.[1,2] Despite its importance, the source of pain remains unclear.[3] To treat OA optimally, knowledge of the source of pain is important since new therapies can be specifically targeted.

An important element in understanding pain is to know which structures produce it inside the knee since the pathology of knee OA involves the whole knee joint.[3] To assess knee structures in vivo, imaging modalities are needed. On radiographs, hallmarks of knee OA such as bony outgrowth and cartilage loss, which are visualised as osteophytes and joint space narrowing, respectively, do not show a consistent association with knee pain.[4] Other potential sources include abnormalities in subchondral bone, ligamentous damage, meniscal injury and synovitis.[5] However, these potential sources cannot be assessed on conventional radiographs. More advanced imaging techniques are needed currently best exemplified by MRI.

Several studies have investigated MRI findings related to pain but to our knowledge, no summarization of data has been performed in a systematic manner. Such a review requires a focused research question, an explicit research strategy and a system to evaluate the quality of evidence.[6] Therefore, we sought to evaluate the relationship between MRI findings in knee OA and knee pain. We summarized eight commonly reported MRI findings: cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition (table 2.1).

Table 2.1 Definitions of the lesions associated with knee OA viewed on MRI.

Lesions	Definition
Cartilage defects	Cartilage abnormalities scored on MRI images using semi-quantitative method or determined using quantitative method.
Bone marrow lesion (BML)	Ill-defined lesions in the medullary space with high signal on T2-weighted imaging or low-signal on T1-weighted imaging scored using semi-quantitative method.
Osteophytes	Focal bony protrusion that extended from bones cortical surface scored for presence or using semi-quantitative scoring methods.
Meniscal abnormalities	Tear of meniscus or meniscus lesion or subluxation scored semi-quantitatively.
Effusion/ synovitis	Effusion: Fluid in synovial space scored for presence or scored using semi-quantitative method. Synovitis: synovial layer scored on the presence of thickening or scored semi-quantitatively. Synovitis and effusion scored together using semi-quantitative method.
Ligaments abnormalities	Tear of ligaments or lesion of the ligaments scored semi-quantitatively.
Subchondral cysts	Marginated circular area filled in with fluid under the cartilage scored for presence or scored using semi-quantitative method.
Bone attrition	Flattening or depression of the articular cortex scored using semi-quantitative method.

2.2. MATERIALS AND METHODS

The present review is systematic review of observational studies. Therefore, we adhered to a protocol developed from a widely recommended method for systematic review/meta-analysis of observational studies (MOOSE).[7] We included studies with data on the association between MRI features of knee OA (exposure of interest) and knee pain (outcome). The following studies were excluded: reviews, abstracts, letters to the editor, case reports, case series and studies concerning study population with other underlying musculoskeletal diseases.

2.2.1. Data sources, searches and extraction

Using the following key words: ‘knee’, ‘knee pain’, ‘MRI’, ‘osteoarthritis’ in combination with all possible key words concerning MRI features we wanted to investigate, we searched the following medical databases up to March 2010: Medline (from 1966), Science Citation Index through Web of Science (from 1945), Embase (from 1980) and, Cumulative Index to Nursing & Allied Health Literature (CINAHL) (from 1982). No language restriction was applied and no search of unpublished studies was performed. Additionally, the reference lists of all relevant identified articles were screened and Google Scholar was searched to find additional papers.

Two reviewers, EY (a PhD student) and MCK (a rheumatologist) independently screened the titles of retrieved references for obvious exclusion and read the remaining abstract to determine eligible studies. Differences were solved by discussion or by consulting a third reviewer (MK, a senior rheumatologist). From eligible papers, information was collected on the following categories: (i) type of study, performed by looking at the method of data analysis (when a study provided data on the association between MRI features change in time with change in pain level in time, the study was considered to be a prospective cohort study; if this analysis was not available, such as in a case-control study, the study was regarded to be of a cross-sectional design); (ii) study population (patient characteristics, size, gender and age); (iii) definition of knee OA; (iv) assessment of MRI findings; (v) assessment of pain; (vi) potential confounders; and (vii) results of the association between MRI features and pain.

2.2.2. Assessment of study quality

Independently, the same two reviewers assessed the methodological quality of included studies using a predefined criteria set which was previously used in systematic reviews in the area of musculoskeletal disorders (table 2.2).[8,9] Several domains were assessed: population, selection bias, assessment of determinants on MRI, assessment of the outcome, follow-up analysis and data presentation.

For each criterion met in the article, a ‘1’ was given; otherwise, a ‘0’ was given. We defined rules on how to assess specific situations. A study could describe multiple MRI features but not all were assessed reproducibly (criterion 5) or using standardized criteria (criterion 6). For such a study, the criteria are scored as a proportion of MRI features which were assessed reproducibly or using standardised criteria from the total MRI features investigated.

Differences in scoring were resolved by discussion or by consulting the third reviewer. Maximum scores possible were 11 for prospective cohort and 9 for cross-sectional study design. The total score for a study (in %) is the total score given for a study divided by the maximum possible score. The mean of the quality scores of all studies, which was 62%, was used to classify studies as high or low quality.

Table 2.2 Criteria for the quality evaluation of the included studies.

Item	Criteria	Applicable for
Study Population: Definition of Study Population		
1.	Sufficient description of characteristics of the study population. Sufficient is when age, sex and settings are mentioned.	C/ CS
Study Population: Selection Bias		
2.	Clear description of selection of study subjects.	C/ CS
3.	Participation rate >= 80% for study population.	C/ CS
Assessment of findings on MRI		
4.	Findings were assessed reproducibly. If multiple findings were assessed, the score will be the number of findings assessed reproducibly divide by all findings studied.	C/ CS
5.	Findings were assessed using validated criteria. If multiple findings were assessed, the score will be the number of findings assessed by using standardized criteria divide by all findings studied.	C/ CS
6.	MRI readers were blinded to clinical findings.	C/ CS
7.	The sequence of scans were unknown to the MRI readers.	C
Assessment of the outcome: Knee Osteoarthritis pain		
8.	Presence of pain was assessed using validated scales.	C/ CS
Follow-up		
9.	No difference in characteristics between withdrawal and completers groups.	C
Analysis and Data Presentation		
10.	Appropriate analysis techniques were used.	C/ CS
11.	Adjusted for possible confounders. At least adjustment should be made for age and sex.	C/ CS

C: prospective cohort studies and CS: cross-sectional studies

2.2.3. Rating the body of evidence

The summary of evidence for each MRI feature was given by using best evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group.[10] This is an alternative to pooling of association sizes when the included studies were heterogenous.[8] The synthesis has five levels of evidence: (1) strong, when general consistent findings were reported in multiple high-quality cohort studies; (2) moderate, when one high-quality cohort study and at least two high-quality cross-sectional studies show general consistent findings or when at least three high quality cross-sectional studies who general consistent findings; (3) limited, when general consistent findings were found in a single cohort study, or in maximum two cross-sectional studies; (4) conflicting, when no consistent findings were reported; and (5) no evidence, when no study could be found. This synthesis puts more weight on a prospective cohort design which is appropriate for our review question since it takes into account the change in determinant (MRI feature) and change in outcome (pain).

Sensitivity analyses by defining other cut-offs (median score of all studies instead of mean) of high quality studies were performed. We also present the number of positive studies without quality assessment to give readers the opportunity to compare this with the best evidence synthesis results. A study that investigated multiple features was counted as a single study for each MRI feature investigated.

A study was regarded as positive if it showed a significant association between an MRI feature and knee pain. When a study included subfeatures of an MRI finding, that is, tear and subluxation for meniscal lesion, the study was regarded as positive when at least one of these showed positive association. Since effusion and synovitis cannot be readily differentiated on non-enhanced MRI, [9,11] we analysed these features together.

2.3. RESULTS

2.3.1. Literature flow

After screening their title, 2144 of 2629 identified references were excluded (figure 2.1). From the 485 remaining references, 19 papers were included. We selected the most recent publication [12] of two publications with overlapping results.[12,13] Four publications [14-17] came from the same authors and used the same patient population.

We therefore selected two of them.[14,16] These two selected studies defined cartilage loss as determinant and pain as outcomes, contradictory to the two others which defined the determinant and outcomes conversely. After additional searching, another three papers were found.[16,18,19] In total, 22 papers were selected. In all, 5 studies reported longitudinal data [12,14,16,20,21] and 17 [18,19,22-36] were cross-sectional studies.

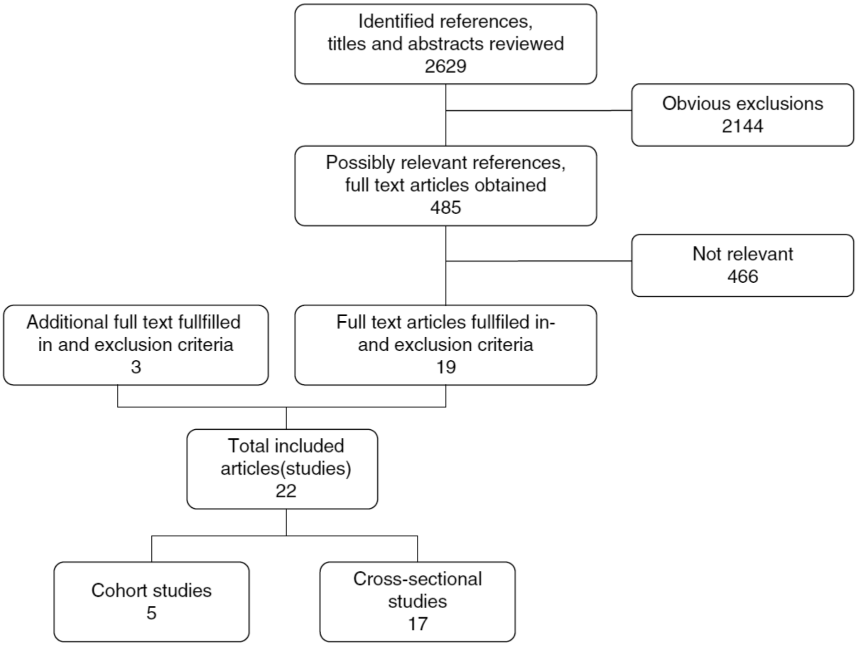

Figure 2.1 Identified references.

2.3.2. Characteristics of included studies

Of the 22 analysed papers, 8 published associations of multiple MRI features (table 2.3), [19,25,26,29,30,32,34,36] the others investigated only a single MRI feature. Of these papers, 10 were results from 3 studies: the Boston Osteoarthritis Knee Study (BOKS) [12,18,22,24,28,33], the Southeast Michigan OA (SEM) cohort [26,34] and the Genetic Arthrosis Progression Study (GARP).[20,29] Most studies used a General Electric MRI system (in 14 publications).[12,13,16,18,19,22-24,26,28,30,32-34] A Siemens MRI system was used in four publications [14,25,27,31] and a Philips MRI system was used in two publications.[20,29] Two studies [35,36] used a 3 T magnetic field system, all others used a 1.5 T system. Only one study [35] used MRI contrast agent.

Patients investigated in the included studies were of both sexes and older than 50 years, except for one which studied women alone with mean age of 47 years (table 2.3).[26] Almost all studies defined knee OA by using clinical and radiographic criteria of American College of Rheumatology, which requires at least knee pain and osteophyte on radiograph. Only five studies defined knee OA purely radiographically.[19,23,26,27,31]

2.3.3. Study quality assessment

We agreed on 212 of 227 (93%) quality assessment items scored. Most disagreement focused on the clarity of description of the study population (criterion 2) and participation rate (criterion 3). Based on quality assessment, the mean of the quality scores of all studies was 61%. In general, many publications either did not assess MRI findings using standardised and validated criteria or they did not inform the reader about this (criterion 5). In many prospective cohort studies the researchers were not blinded for the time order of MRI scans (criterion 7) and differences between withdrawal and completed groups were not described (criterion 10). In cross-sectional studies, the most common limitations were participation rate (criterion 3) and lack of adjustment of possible confounders such as age and sex (criterion 11).

Table 2.3 Characteristics of included studies (listed alphabetically by first author surname).

Studies	Study population	Features assessed	Pain assessment	Statistical analysis	Quality score (%)
Cohort studies					
Hill, 2007[12]	Knee OA patients (ACR criteria). n=270 (42% female); age 67±9 years[1]. Boston osteoarthritis of the knee study (BOKS), USA.	Effusion/ synovitis	VAS	Linear regression	68
Kornaat, 2007[20]	Generalized OA patients. n=182 (86% female); median age 60 years (range 43 to 77). Genetics, arthrosis progression (GARP) study, The Netherlands.	BML	WOMAC pain	Linear mixed model	64
Pelletier, 2008[21]	Knee OA patients (ACR criteria) from outpatient rheumatology clinic. n=27 (52% female); age 64±9.6 years. Canada.	Synovitis	WOMAC and VAS pain	Spearman correlation	36
Raynauld, 2004[14]	Knee OA patients (ACR criteria). n=40 (88% female); age 62±8 years. Canada.	Cartilage	WOMAC and VAS pain	Spearman correlation	64
Wluka, 2004[16]	Knee OA patients (ACR criteria). n=132 (54% female); age 63 years (range 41 to 86). Australia.	Cartilage	WOMAC pain	Spearman correlation	64
Cross sectional studies					
Anandacoo-marasamy, 2009[35]	Obese knee OA patients from general population (ACR criteria). n=77 (68% female); age: 51±12.7 years. Sydney, Australia.	Cartilage	WOMAC pain	Spearman correlation	67
Amin, 2008[22]	BOKS, USA. *See above.* n =265 (43% female); age 67±9 years.	ACL tear	VAS	Student t-test	67
Bhattacharyya, 2003[18]	Cases: BOKS, USA. *See above.* n=154, age 65 years. Controls: no knee pain. n= 49; age 67 years.	Meniscal tear	VAS	Student t-test	67
Dunn 2004[23]	Patients suspected for clinical OA. n=55 (55% female); age 63±3 years. USA.	Cartilage	WOMAC pain	Spearman correlation	22
Felson, 2001[24]	BOKS, USA. *See above.* n= 401 (33% female in knee pain group, 48% in no pain group); age 62 years (range 22 to 91).	BML	Presence/ absence of pain	Logistic regression	75
Fernandez -Madrid, 1994[25]	Case: Knee OA patients (ACR criteria). Detroit, USA. n= 52 (67% female); age 55±14 years. Control: general population. n=40 (62% female); age 49±15 years.	Cartilage, osteophytes, subchondral lesions, effusion/ synovitis, meniscal tears	Presence/ absence of pain	Chi-squared test	72
Hayes 2005[26]	Four groups (each n=30, 100% female): 1. no pain, no radiographic knee OA; age 45±1 years 2. no pain, radiographic knee OA; 46±1 years. 3. pain, no radiographic knee OA; 47±1 years. 4. pain, radiographic knee OA; 47±1 years. Southeast Michigan Osteoarthritis cohort, USA.	Cartilage, osteophytes, subchondral cysts, BML, effusion/ synovitis, meniscal tear, ACL tear	Presence/ absence of pain	Fisher exact test of general association	56

Hernández-Molina, 2008[27]	Knee OA patients (K&L ≥2). n =1273 (48% female); age: 65±9 years. Framingham OA study cohort, Massachusetts, USA.	Bone attrition	Presence/ absence of pain	Chi-squared test	78
Hill, 2005[28]	Cases: BOKS, USA. *See above.* n=360 (33% female); age 68 years. Controls: no knee pain. n=73, 65% with K&L ≥2 and JSN≥1 (57% male) 66 years.	ACL tear	Presence/ absence of pain	Chi-squared test	50
Kornaat, 2006[29]	GARP. *See above.* n=205 (80% female); median age 60 years (range: 43 to 77).	Cartilage, osteophytes, subchondral cysts, BML, effusion, meniscal defects	Presence/ absence of pain	Logistic regression	78
Link, 2003[30]	Knee OA patients (ACR criteria). n=50 (60% female); age 64±11 years.	Cartilage, BML, meniscal tear, ACL tear.	WOMAC pain	Wilcoxon rank sum test	47
Lo, 2009[36]	Knee OA patients (Knee pain or stiffness and osteophytes OARSI atlas score 1 to 3). n=160 (50% female); age 61±9.9. Osteoarthritis initiative (OAI).	BML, effusion/synovitis	WOMAC pain	Logistic regression	78
Pelletier, 2007[31]	Knee OA (radiographic) from general population. Subset from clinical trial on Risendronate in North America. n=110 (64% female); age 62±7 years.	Cartilage	WOMAC pain	Spearman correlation	39
Phan, 2006[32]	Knee OA patients (ACR criteria), n= 34 and general population, n=6 (60% female); age: 58±16 years	Cartilage, BML	WOMAC pain	Correlation not specified	67
Sengupta, 2006[33]	BOKS. *See above*. n=217 (30% female); age 67±9 years.	Osteophytes	10-point pain scale	Logistic regression	78
Sowers, 2003[34]	Southeast Michigan Osteoarthritis cohort, USA. *See above*.	Cartilage, BML	VAS pain	Wilcoxon or Maentel-Haenszel test of general association	78
Torres, 2006[19]	Knee OA patients (K&L ≥2 and 'a little difficulty' in one or two WOMAC physical function scale). n=143 (88% female); age 70±10 years.	Cartilage, osteophytes, bone cysts, bone attrition, BML, synovitis, meniscal tears, ligament abnormalities (MCL, LCL, and ACL)	VAS pain	Median quantile regression	78

ACR clinical and radiographic criteria requires knee pain and osteophytes on radiograph.[50]
[1] Mean age, otherwise specified.
ACL, anterior cruciate ligament; ACR, American College of Rheumatology; BMI, body mass index; BML, bone marrow lesion; JSN, joint space narrowing; K&L, Kellgren and Lawrence Osteoarthritis Scoring System for knee radiographs; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; n, number of study population; OA, osteoarthritis; VAS, visual analogue scale.

2.3.4. Association between MRI features and pain (best-evidence synthesis) (table 2.4)

Cartilage defect

Six studies [19,26,29-32] investigated cartilage defects using semiquantitative scores, five [14,16,23,25,34] used quantitative methods and one used quantitative method on contrast-enhanced MRI.[35] The level of evidence on the association between cartilage defects and pain was conflicting: three [16,19,34] of five high-quality studies showed a positive association with pain. When all 12 studies which investigated cartilage defects [14,16,19,23,25,27,29-32,34,35] were summarised, 50% showed a positive association independent of study quality.

Bone marrow lesions

The evidence about the association between BML and pain was moderate. Four [19,24,34,36] of five high-quality studies showed an association between BML and pain. One high-quality cohort study showed no association.[20] Three of the four high-quality cross-sectional studies that demonstrated a positive association presenting an odds ratio (OR) as quantitative measure of association. The OR ranged from 2.0 (adjusted for effusion and synovitis) [36] to 5.0 (unadjusted, 95% CI 2.4 to 10.5).[34] One study reported a β coefficient of 3.72 (95% CI 1.76 to 5.68).[19] When all eight studies investigating BML [19,20,24,26,30,32,34,36] were taken into account 63% reported a positive association between BML and pain.

Osteophytes

Neither of the two high-quality studies showed a positive association between osteophytes with pain.[29,33] According to best evidence synthesis this gives limited level of evidence on the no association between osteophytes and knee pain.

Meniscal lesions

Only one [19] of three high-quality cross-sectional studies showed a positive association resulting in a conflicting level of evidence for the association between meniscal lesions and pain.[18,19,29] When all studies were taken into account; 33% showed a positive association.

Synovitis/joint effusion

A moderate association was found for effusion/synovitis, since all four [12,19,29,36] high-quality studies showed a positive association. One of which was a high-quality cohort study.[12] This study performed separate analyses for effusion and synovitis: the analysis between effusion and pain showed no association whereas the association between synovitis and pain was positive. We regarded this study as positive, because we deemed a study was as a positive study when at least one of the subfeatures showed a positive association. Four high-quality studies reported quantitative measures of association. Three reported the OR of having pain when effusion/synovitis was present, ranging between 2.6 (adjusted for synovitis and BML) [36] and 10.0 (adjusted for age, sex BMI and intrafamily effects, 99% CI 1.13 to 149).[29] One other study reported β regression of 9.82 (95% CI 0.38 to 19.27).[19] When no quality assessment was performed, 86% of included studies [12,19,21,25,26,29,30,36] showed a positive association with pain.

Ligament disease

Two studies [28,30] classified ligament abnormalities as presence or absence of tears, and three studies [19,22,26] used semiquantitative scores. Since only two high-quality studies [19,22] were available, which showed positive association, this resulted in a limited level of evidence for a positive association between ligament abnormalities and pain. When all five studies [19,22,26,28,30] were taken in account, only 40% showed a positive association.

Subchondral cyst

Subchondral cysts were not associated with pain. Two high-quality studies showed no association and this resulted in a limited level of evidence.[19,29]

Bone attrition

Conflicting evidence was found on the association between bone attrition and pain. One [19] of two high-quality cross-sectional studies, [19,27] showed a positive association.

Table 2.4 Best evidence synthesis (MRI features were arranged from top to bottom according to the number of studies included).

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/total (%)	
		Crude	Adjusted		All	High quality
Cartilage defects (level of evidence: conflicting)						
Scored using semi-quantitative scores						
Pelletier[31]	CS	r= 0.09, p=0.38	-	na	6/12 (50%)	3 (1C, 2CS) / 6 (2C, 3CS) (50%)
Phan[32]	CS	r= not mentioned, NS	-	na		
Torres[19]	CS	β=1.03 (95% CI 0.6 to 1.5)	0.53 (0.08 to 0.98)	age and BMI		
Hayes[26]	CS	+-ve, p=0.001	-	na		
Kornaat[29]	CS	-	OR=1.12 (99% CI 0.4 to 3.2)	age, sex, BMI, intrafamily effects		
Link[30]	CS	+-ve, p<0.05	-	na		
Scored quantitatively						
Raynauld[14]	C	r= -0.25, NS (WOMAC) r= 0.12, NS (VAS)	-	na		
Wluka[16]	C	r= 0.28, +-ve, p=0.002	-	na		
Fernandez-Madrid[25]	CS	NS	-	na		
Sowers[34]	CS	+-ve, p<0.0001	-	na		
Dunn[23]	CS	+-ve, p<0.05	-	na		
Scored using other methods (i.e. quantitatively after giving contrast agent)						
Anandacoomarasamy[35]	CS	r= -0.21, p=0.07	-	na		

Bone Marrow Lesion (level of evidence: moderate)						
Kornaat[20]	C	-	mean difference (increasing BML)=2 (95% CI -8 to 11)	age, sex, BMI, intrafamily effects	5/8 (63%)	4 (CS) / 5 (1C, 4CS) (80%)
Hayes[26]	CS	+-ve, p=0.001	-	na		
Felson[24]	CS	-	OR=3.31 (95% CI 1.5 to 7.4)	age, sex, radiological and effusion score		
Link[30]	CS	p>0.05	-	na		
Lo[36]	CS	+, RR BML scores vs. no BML= 1: 1.3 2: 2.1 3: 2.3 p for trend=0.0009	+, 1: 1.2 2: 1.9 3: 2.0 p for trend 0.006	effusion and synovitis		
Phan[32]	CS	r is not mentioned, NS	-	na		
Sowers[34]	CS+	OR=5.0 (95% CI 2.4 to 10.5)	-	na		
Torres[19]	CS+	β=5.0 (95% CI 3.0 to 7.0)	3.72 (1.8 to 5.7)	age and BMI		
Osteophytes (level of evidence: limited)						
Presence						
Fernandez-Madrid[25]	CS	NS	-	na	2/6 (33%)	0 / 2 (CS) (0%)
Hayes[26]	CS	+-ve, p<0.001	-	na		
Kornaat[29]	CS	-	OR=1.05 (99% CI 0.4 to 2.9)	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Torres[19]	CS	β= 1.2 (95% CI 0.6 to 1.7)	β= 0.5 (0.07 to 0.94)	age and BMI		
Signal strength						
Sengupta[33]	CS	-	PR=0.94 (0.8 to 1.1)	age, sex, BMI		

Table 2.4 Continued

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/total (%)	
		Crude	Adjusted		All	High quality
Meniscal lesion (level of evidence: conflicting)						
Bhattacharyya[18]	CS	-	p=0.7	age	2/6 (33%)	1 / 3 (CS) (33%)
Fernandez-Madrid[25]	CS	NS	-	na		
Hayes[26]	CS	+-ve, p=0.001	-	na		
Kornaat[29]	CS	-	Tears: OR=1.26 (99% CI 0.6 to 2.7) Subluxation: OR=1.03 (99% CI 0.5 to 2.2)	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Torres[19]	CS	Tears: β= 3.3 (95% CI 0.9 to 5.8) Subluxation: β= 15.0 (95% CI -0.3 to 30.3)	Tears: 2.0 (0.6 to 3.4) Subluxation: 2.22 (-6.9 to 11.3)	age and BMI		

Effusion and synovitis (level of evidence: moderate)						
Hill[12]	C	-	Effusion: OR=1.2 (95% CI -8.1 to 10.5) Synovitis: OR=3.2 (95% CI 1.04 to 5.3)	age, sex, BMI, cartilage score at baseline, effusion score, BML score, change in effusion and BML score.	6/8 (80 %)	4 (1 C, 3 CS) / 4 (1C, 3 CS) (100%)
Fernandez-Madrid[25]	CS	Effusion: +-ve, p<0.001 Synovitis: NS	- -	na		
Hayes[26]	CS	Effusion: +-ve, p<0.001 Synovitis: +-ve, p<0.001	- -	na		
Kornaat[29]	CS	-	Effusion: OR=10.0 (99% CI 1.1 to 149)	age, sex, BMI, intrafamily effects		
Link[30]	CS	Effusion: p>0.05	-	na		
Lo[36]	CS+	Effusion: RR BML scores vs. no BML= 1: 1.8 2: 2.4 3: 3.1 p for trend<0.0001 Synovitis: 1: 1.9 2: 1.9 3: 2.3 p for trend 0.20	 1: 1.7 2: 2.0 3: 2.6 p for trend=0.0004 Synovitis: 1: 1.4 2: 1.5 3: 1.9 p for trend= 0.22	synovitis and BML		
Torres[19]	CS	β= 15.0 (95% CI -8.2 to 38.2)	9.8 (0.4 to 19.3)	age and BMI		
Pelletier[21]	C	Effusion: r=0.07,+-ve, p=0.71 (WOMAC) r=0.01,+-ve, p=0.93 (VAS)	-	na		

Table 2.4 Continued

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/total (%)	
		Crude	Adjusted		All	High quality
Knee ligament abnormalities (level of evidence: limited)						
Amin[22]	CS	-	ACL: +-ve, p<0.05	age, sex, BMI, and cartilage scores	2/5 (40%)	2 / 2 (CS) (100%)
Hill[28]	CS	ACL: +-ve, p=0.0004	-	na		
Link[30]	CS	ACL: p>0.05 MCL and LCL: p>0.05	-	na		
Torres[19]	CS	β (95% CI) ACL: 5.0 (-13.0 to 23.0) MCL: 0 (-11.9 to 11.9) LCL: 15.0 (95% CI -8.2 to 38.2)	ACL: 6.8 (-5.4 to 19.0) MCL: -6.10 (-14.0 to 1.7) LCL: 29.5 (17.8 to 41.1)	age and BMI		
Hayes[26]	CS	ACL and PCL: p=0.23 MCL and LCL, p=0.86	-	na		
Subchondral cysts (level of evidence: limited)						
Hayes[26]	CS	+-ve, p<0.001	-	na	1/5 (20%)	0/ 2 (CS) (0%);
Kornaat[29]	CS	-	OR=1.71 (99% CI 0.8 to 3.6)	age, sex, BMI, intrafamily effects		
Link[27]	CS	p>0.05	-	na		
Fernandez-Madrid[25]	CS	NS	-	na		
Torres[19]	CS	β=2.50 (95% CI -0.4 to 5.4)	0.82 (-0.5 to 2.1)	age and BMI		

Bone attrition (level of evidence: conflicting)						
Hernández-Molina[27]	CS	OR=2.1 (95% CI 1.4 to 3.4)	1.2 (0.7 to 2.0)	age, sex, BMI, K&L grade, presence of BML and effusion	1/2 (50%)	1/ 2 (CS) (50%);
Torres[19]	CS	β=3.3 (95% CI 1.8 to 4.9)	1.9 (0.7 to 3.1)	age and BMI		

Author's name in *italic* indicates high-quality studies; 'positive' in front of p values indicates significant positive association sizes.
r: (Spearman's or Pearson's) correlation coefficient between MR feature of interest and pain in continuous scale (WOMAC pain subscale or VAS); in a cohort study the correlation coefficient showed the association between changes of the MRI features with the changes in pain during the follow-up. OR, odds of having pain (in cross-sectional studies) or increasing pain (in cohort studies) when a MRI feature is present or increasing comparing to the odds when MRI feature is absent. β is regression coefficient representing the increase in knee pain severity associated with increase in lesion score, PR, prevalence (odds) ratio.
ACL, anterior cruciate ligament; BMI, body mass index; BML, bone marrow lesion; C, cohort, CS, cross-sectional studies; K&L, Kellgren and Lawrence; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; NA, not applicable; NS, not significant; PCL, posterior cruciate ligament; VAS, Visual analogue scale; WOMAC, Western Ontario and McMaster Scoring system.

2.3.5. Sensitivity analysis

When we used median score of all studies instead of mean score as the cut-off of high-quality studies, the level of evidence of the association of all MRI finding investigated remained the same. The number of positive studies without quality assessment is shown in table 2.4.

2.4. DISCUSSION

Pain is the most disabling symptom of OA. Knowledge about the structures that cause pain is crucial, because in the future it may be possible to specifically target interventions. For a long time, research on the structural cause of pain has been focused on cartilage defects, even though cartilage does not have pain fibres.[3] Further, research on structures that produce pain in the knee was hampered by the limited ability of radiographs to visualise knee structures extensively. MRI has been shown to be superior to plain films. It demonstrates the whole joint organ. Since several initial reports seemed positive about the association between MRI findings and pain, we therefore investigated the evidence between the MRI findings and knee pain in patients with knee OA. Our findings will be relevant to researchers, clinician and radiologists reporting MRI studies.

We identified a moderate level of evidence for a positive association for BML and effusion/synovitis with pain in knee OA. The level of evidence was limited for a positive association for knee ligamentous abnormalities. We found limited levels of evidence for no association for osteophytes and subchondral cysts. Conflicting levels of evidence were found for cartilage defects, meniscal lesions and bone attrition. We did not investigate studies found during the literature search which investigated features beyond the scope of this review: patella alignment, [37] peripatelar and other periarticular lesions, [38] popliteal or synovial (Baker's cyst).[13,26,29]

In our review, we used a priori defined qualitative levels of evidence to reach a summary. We consider this as a strength because we provide an alternative to quantitative statistics, which could not be calculated as the topic of our review included several aspects of studies that were heterogenic. However, simply counting positive studies also has several drawbacks. It does not take into account the size of the studies, and the decision on 'positive or negative' studies was based only on statistical significance. In meta-analysis, it is theoretically possible that individual studies are negative but the pooled effect is positive.[39] Another technical limitation of our review is the use of quality scores to assess the methodological quality of the studies. It could be that when different quality score sets were used, the interpretation of the results could be influenced.[40] Other limitations of this review mostly reflect the limitations of the studies investigated. First, no publication bias could be assessed using a funnel plot due to the limited number of studies that reported their results in relative risk (RR) or OR.[41] Therefore, we do not know whether preferentially positive findings were published. Second, the quality of included studies was not excellent. There are several obvious examples of limitations of the studies. MRI scan interpretation is by nature subjective, as few, if any, quantitative methods exist. Attempts at standardization may not be generally used. Also, most scans were read unblinded to order. It is possible that MRI readers define the later findings as more severe than the first findings. This could lead to misclassification.

The moderate associations found in the review have the consequence that more research is needed.[42] Epidemiological studies about BML and effusion/synovitis could strengthen the levels of association. An ideal epidemiological study design would be a case-crossover study where individual MRI findings in the presence of knee pain at one time point are compared with MRI findings in the same patient without knee pain at another time point. The ideal data analysis would give an association size and permit adjustment for confounders, including age and sex, and also for other MRI features when multiple MRI findings are studied simultaneously.

The causal relationship between BML and effusion/synovitis and pain in knee OA needs further study. Our knowledge is now limited to the fact that BML, defined as ill-defined hyperintensities on T2-weighted MRI, [43] comprises normal tissue, oedema, necrosis and fibrosis in histological slices.[44] Further, although knee OA is not considered as an inflammatory arthritis per se, research on the role of inflammation in knee OA and the potential use of anti-inflammatory treatments in knee OA should also be pursued in the light of the possible association between effusion/ synovitis with knee pain in knee OA. Evaluation of effusion and synovitis can be improved by using contrast enhancement, since it can highlight inflammation and improve the distinction between synovitis and effusion.[12,19] Gadolinium contrast diffusion is affected in synovitis tissue, where the blood flow and permeability are changed.[45] In the present review, no included papers performed contrast-enhanced MRI.

Beyond the knee itself further research needs to be focused on the origin of pain in OA and representation in the central nervous system. Some observations have shown that pain in arthritis is also characterised by abnormal pain response (hyperalgaesia) [46] and functional MRI has the potential to study hyperalgaesia and other pain response.

Knowing which structures in the knee are associated with knee OA will add to our understanding of OA and, in the long term, will lead to rational therapeutic targets for OA. This will mean improvement in patient care, since at this moment the therapeutic options against OA are limited.[47] At present, the clinical implication of BML is not clear, despite being a common finding in knee OA, being present in 78% of patients with knee OA with pain and in 30% of patients with knee OA without pain.[24] BML is plainly not pathognomonic of knee OA as it is also found in a range of conditions such as trauma, osteoporosis and rheumatoid arthritis.[48] Moreover, BML is also not a static finding. Almost every BML in knee changes in size over a period of 3 months.[49] The clinical implications of effusion/ synovitis may be clearer, since they might permit the potential use of anti-inflammatory drugs in treatment of OA. Effusion/ synovitis is common in knee OA. Moderate effusion being seen in 36% of patients with knee OA and synovitis present in (84%) of knees.[26]

The finding that ligamentous abnormalities may associate with pain is of special interest. While the exact aetiology and management of these finding remains unclear it may be that surgical intervention could in theory be aimed at repair of these structures to alleviate pain. However, based on present knowledge, surgical intervention for symptomatic treatment is not currently indicated.

In summary, this systematic review has shown that BML and effusion/synovitis were associated with knee OA pain. However, the level of evidence is moderate and these features need to be explored further.

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