


REVIEW

Associations between markers of inflammation and altered pain perception mechanisms in people with knee osteoarthritis: a systematic review

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ABSTRACT

To provide an extensive review on the associations between knee inflammation and altered pain perception mechanisms in people with knee osteoarthritis (OA). MEDLINE, Web of Science, EMBASE and Scopus were searched up to 13 December 2022. We included articles reporting associations between knee inflammation (measured by effusion, synovitis, bone marrow lesions (BMLs) and cytokines) and signs of altered pain processing (assessed by quantitative sensory testing and/or questionnaire for neuropathic-like pain) in people with knee OA. Methodological quality was evaluated using the National Heart, Lung and Blood Institute Study Quality Assessment Tool. Level of evidence and strength of conclusion were determined using the Evidence-Based Guideline Development method. Nine studies were included, comprising of 1889 people with knee OA. Signs of greater effusion/synovitis may be positively associated with lower knee pain pressure threshold (PPT) and neuropathic-like pain. Current evidence could not establish an association between BMLs and pain sensitivity. Evidence on associations between inflammatory cytokines and pain sensitivity or neuropathic-like pain was conflicting. There are indications of a positive association between higher serum C reactive protein (CRP) levels and lower PPT and presence of temporal summation. Methodological quality varied from level C to A2. Signs of effusion/synovitis may be positively associated with neuropathic-like pain and pain sensitivity. There are indications of a possible positive association between serum CRP levels and pain sensitivity. Given the quality and the small amount of included studies, uncertainty remains. Future studies with adequate sample size and follow-up are needed to strengthen the level of evidence. PROSPERO registration number: CRD42022329245.

INTRODUCTION

Osteoarthritis (OA) is a leading cause of chronic disability and carries a serious health and economic burden.¹ The knee is the most affected joint accounting for approximately 85% of the burden of OA worldwide² (about 365 million people globally).³ Knee OA is

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Knee osteoarthritis is characterised by low-grade chronic inflammation.
- ⇒ Inflammatory signs (eg, effusion, synovitis and proinflammatory cytokines) are weakly or moderately associated with pain intensity.
- ⇒ Pain in osteoarthritis is complex and characterised by nociceptive and neuropathic components along with possible pain sensitivity (peripheral and/or central sensitisation).

WHAT THIS STUDY ADDS

- ⇒ Signs of effusion/synovitis may be positively associated with neuropathic-like pain and signs of pain sensitivity.
- ⇒ There are indications of a possible positive association between serum C reactive protein levels and pain sensitivity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Understanding how different inflammatory markers are related to symptoms is critical to devise new treatments and will ultimately lead to improvement of therapeutic approaches and better pain management.

a multifactorial disease of the whole joint organ that presents a multitude of pathological changes involving cartilage degradation, osteophyte formation, osteochondral unit remodelling and joint inflammation.⁴ Clinically, patients with OA experience stiffness, pain and loss of function.⁵ Chronic pain is the dominant symptom and the main drive for patients to seek medical help.⁶ Unfortunately, to date, there is no effective therapy that guarantees an effective and long-lasting symptomatic relief nor a stop to the progression of OA.⁷

Traditionally, OA pain was considered and investigated as purely nociceptive arising

from tissue damage. However, evidence on associations between tissue damage and pain is conflicting.⁸ Furthermore, a substantial portion of patients (~20%) suffer from persistent pain after the removal of damaged tissue by undergoing total knee arthroplasty (TKA).⁹ These observations led to an emerging growing body of evidence showing how various pain mechanisms contribute to pain.¹⁰ Pain in OA is characterised by nociceptive and neuropathic components along with possible sensitisation (peripheral and/or central).^{11,12} A subgroup of patients with knee OA (~40%) describe their pain as a sensation of burning, electric shock, numbness and itch, attributable to a neuropathic cause.¹³ Neuropathic pain is defined as ‘pain caused by a lesion or disease of the somatosensory system’.¹⁴ As sensitisation may occur in the absence of actual tissue damage of the somatosensory system (requirement to fulfil the definition of neuropathic pain),¹⁴ the new term ‘nociplastic’ pain was recently introduced.¹⁵ Modern screening tools can identify these pain characteristics attributable to features of altered pain perception mechanism.¹⁶ Neuropathic-like pain symptoms can be identified using patient-reported outcome measures, such as the painDETECT Questionnaire,¹⁷ the Neuropathic Pain Questionnaire (NPQ),¹⁸ the Douleur Neuropathique-4 (DN4)¹⁹ and the Leeds Assessment of Neuropathic Symptoms and Signs.²⁰ Altered pain processing mechanisms can be evaluated by quantitative sensory testing (QST), often reported as the gold standard for quantification of somatosensory abnormalities.^{21,22} QST involves a series of psychophysical techniques that quantify somatosensory-evoked responses to noxious or innocuous stimuli in experimental settings to identify possible dysfunction of the somatosensory system.²³ Localised pain, triggered by experimental stimuli on the affected joint, is associated with peripheral sensitisation, whereas regional or widespread pain at a site adjacent to or at a distance from the site of origin suggests a combination of peripheral and central sensitisation.^{12,24} The most common QST modalities include pain pressure threshold (PPT) (to test for widespread hyperalgesia) and/or temporal summation (TS) (to assess spinal hyperexcitability) and/or conditioned pain modulation (CPM) (to assess a descending inhibitory pathway).²⁵

Due to the complexity of OA pain, the underlying mechanisms have long been unclear, but it is now known that the typical low-grade chronic inflammation of the arthritic joint might be involved in pain generation or altered pain perception.^{26,27} Inflammation of richly innervated structures, such as the synovial membrane (termed synovitis) or lesions in the subchondral bone (termed bone marrow lesions (BMLs)), can contribute to or has been associated with pain.^{28,29} Both synovitis³⁰ and BMLs^{31,32} are sites of proinflammatory mediators expression. Evidence suggests that proinflammatory cytokines, such as interleukin (IL)-6, IL-1 β and tumour necrosis factor- α (TNF- α), are not only mediators of joint inflammation and further degeneration, they can also

activate nociceptors leading to increased responsiveness to stimulation.^{33,34} A permanent state of proinflammatory environment within the joint may facilitate a continuous activation of nociceptors, which may result in sensitisation and/or neuropathic-like pain.³⁴

In a previous systematic review, we concluded that different inflammatory aspects are associated with pain in patients with knee OA but the strength of this association did not exceed the moderate level and the level of evidence ranged from limited to moderate.³⁵ However, we mainly focused on pain intensity (typically measured with self-reported pain tools such as Visual Analogue Scale, Numerical Rating Scale or questionnaires). With this work, we intend to go beyond the mere pain intensity aspect by focusing on studies presenting data on experimental measures of pain (QST) or neuropathic-like pain. In the last years, several studies attempted to better understand the relationship between inflammation and altered pain processing in patients with knee OA. However, no extensive synthesis is available in the literature. The aim of this work is to systematically review and summarise the scientific literature on the association between markers of inflammation and altered pain processing in patients with knee OA.

METHODS

Design

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).³⁶ The PRISMA checklist can be found in the online supplemental file. The protocol for this review was registered on PROSPERO (registration number: CRD42022329245). Papers reporting associations between inflammation (exposure) and experimental measures of pain (QST) and/or neuropathic-like pain (outcome) in patients with knee OA (population) were included.

Data sources and study selection

Four different databases were consulted (from inception until 13 December 2022): MEDLINE, Web of Science, EMBASE and Scopus. The full search strategy is reported in the online supplemental material. After de-duplication, two reviewers (PD and HM) independently screened the papers based on title and abstract (percentage of agreement 97%) using the Rayyan online tool.³⁷ Conflicts were resolved by discussion and in case of remaining disagreement, a third reviewer (PC) was consulted. The remaining records were independently screened by the same two reviewers (PD and HM) on full text and for unresolved disagreements, the third reviewer (PC) was consulted. Additionally, the reference lists of eligible studies were hand searched for possible relevant records. The flow chart (figure 1) provides more details on the full screening process.

Eligibility criteria

Papers were eligible if the following inclusion criteria were met: (1) original observational studies (cross-sectional,

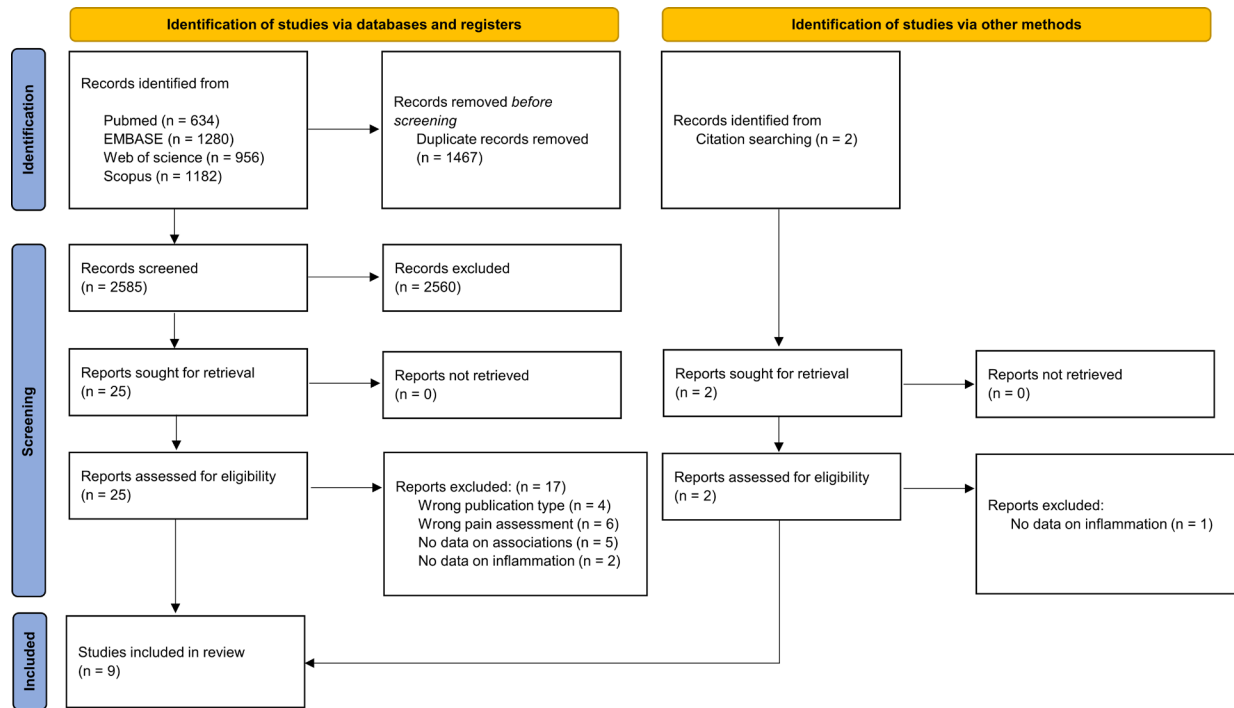


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram documenting the search and screening process.

case-control and cohort studies); (2) written in English, Dutch, French, German or Italian; (3) investigating people with knee OA; (4) the results report an association between (i) inflammation investigated through (a) medical imaging (ie, evaluation of effusion/synovitis, BMLs assessed by MRI and/or ultrasound), (b) synovial biopsy (evaluation of synovitis by synovial tissue analysis), (c) circulating biomarkers (biomarkers—cytokines, C reactive protein (CRP) found in blood samples, synovial fluid or urine); (ii) altered pain processing assessed by QST (ie, PPT, CPM and TS) and/or (iii) neuropathic-like pain assessed by questionnaires (ie, painDETECT, DN4 and NPQ). Interventional studies were included if associations between inflammation and pain sensitivity were reported from analysis of baseline data. Other study designs were excluded. Studies including patients with other inflammatory joint diseases (eg, rheumatoid arthritis), presence of other comorbidities per inclusion criteria or multiple OA cohorts (eg, including patients with knee OA and patients with hip OA) were excluded if data from patients with knee OA could not be pooled separately.

Data extraction

From included papers, two reviewers (PD and HM) extracted the following information: (1) author, publication year and country; (2) study design (when a cohort study only provided baseline data on the association between inflammation and pain sensitivity, the paper was considered to be a cross-sectional); (3) patient characteristics (sex, age and body mass index (BMI)); (4) sample size, definition of knee OA, symptoms duration and OA duration; (5) inflammation assessment; (6) assessment of

experimental measures of pain (QST) or neuropathic-like pain; (7) statistical analysis; (8) potential confounders; (9) overall quality based on risk of bias (RoB) assessment; and (10) results of the association between inflammation and experimental measures of pain and/or neuropathic-like pain.

Risk of bias

The RoB assessment was performed independently by the same reviewers (PD and HM) (percentage of agreement 92%) using the National Heart, Lung and Blood Institute (NHLBI) Study Quality Assessment Tool.³⁸ The NHLBI is a study design-dependent tool, consisting of 14 items that evaluate potential methodological flaws (eg, patient selection, adjustment for confounders, study power), and it was previously used in systematic reviews on OA.^{37, 39} The reviewers answered each question with yes, no or other (ie, cannot determine, not applicable, not reported). Differences in scoring were resolved by consulting the third reviewer (PC). A summary score was calculated based on the number of ‘yes’ selected divided by the total amount of items assessed (excluding the not applicable). Final judge of each study was determined according to the following standardisation: <7=high RoB (poor quality), 7–10=moderate RoB (fair quality), 11–14=low RoB (good quality).⁴⁰

Best evidence synthesis

Due to high heterogeneity across papers, it was not indicated to perform a meta-analysis and instead a qualitative evidence synthesis was performed. Level of evidence and strength of conclusion were determined using the Evidence-Based Guideline Development method.⁴¹ Each

Table 1 EBRO classification of the study results according to the level of evidence and definition of level of conclusion assigned per outcome

Level of evidence	
A1	Systematic reviews and meta-analyses, based on minimally 2 independent A2 studies
A2	Prospective cohort studies with sufficient sample size and follow-up; adequately controlled for confounding factors and precluding selective loss to follow-up
B	Prospective cohort studies, but lacking the quality criteria of A2. Retrospective cohort studies and case-control studies
C	Non-comparative studies
D	Expert opinion
Level of conclusion	
1	One A1 or at least two independent A2 studies that support each other's conclusions and do not show conflicting evidence
2	One A2 or at least two independent B studies that support each other's conclusions and do not show conflicting evidence
3	One B or at least two C studies that support each other's conclusions and do not show conflicting evidence
4	Research at level C or two or more independent studies at higher level that do not support each other's conclusions and show conflicting evidence
Consensus	There is no evidence, but consensus (level D)
No conclusions	There is no evidence and no consensus
EBRO, Evidence-Based Richtlijn (Guideline) Ontwikkeling (Development).	

included study was graded for a level of evidence ranging from D to A1, depending on evidence-based medicine domain, study design and individual methodological quality. The strength of conclusion (levels 1–4) was determined to different outcome levels, taking into account the composition of the respective levels of evidence and consistency of their results (table 1).

RESULTS

Literature search and characteristics of included studies

The initial search strategy resulted in 4052 records of which 1467 duplicates were removed and 2560 excluded based on the screening on title and abstract. After screening 25 on full text, 8 studies remained and another 1 was included through citation hand searching. Finally, a total of 9 studies with 1889 participants were included in this review.

The included studies consisted of seven cross-sectional studies,^{42–48} one case-control⁴⁹ and one study reporting longitudinal cohort data.⁵⁰ Patients' characteristics, assessments of inflammation and pain sensitivity, and statistical analysis are reported in detail in table 2. Overall, the majority of the patients in the included studies are represented by women, with one study reporting data of only female patients. Mean age ranges between 65 and 75 years and consists of mainly overweight patients with a mean BMI ≥ 28 kg/m². Different definitions of OA were reported. Six papers used the American College of Rheumatology (ACR) criteria^{42 43 45–48} and five of these also included the Kellgren-Lawrence radiographic grading system to diagnose knee OA.^{42 43 45 47 48} Only one study⁴⁶ specified which ACR criteria were used (ie, clinical, clinical/radiographic or clinical/laboratory). One study included patients scheduled for TKA⁴⁹ and one study

used data from individuals with knee OA (31% with radiographic evidence of knee OA at baseline) or with specific risk factors for developing knee OA.⁵⁰

Inflammation was assessed by either MRI, blood samples and/or synovial fluid. Four articles^{46 47 49 50} used non-contrast-enhanced MRI to semiquantitatively assess effusion/synovitis, with two of them reporting measurements of BMLs as well.^{47 50} Only one study assessed synovitis using contrast-enhanced MRI.⁴⁶ A variety of inflammatory wet biomarkers were investigated in six studies^{42–46 48} of which TNF- α and IL-6 were most commonly reported. The majority of these studies obtained data from blood sample analysis with only two articles analysing synovial fluid.^{45 46}

Altered pain processing was assessed by QST in six studies.^{42–44 47 49 50} Pain sensitivity was primarily assessed using PPT.^{42–44 47 49 50} To evaluate pain sensitisation, one study used TS⁵⁰ and another study combined TS and CPM.⁴² Presence of neuropathic-like pain was assessed by questionnaires in three studies.^{45 46 48} The three studies assessing presence of neuropathic-like pain applied the painDETECT Questionnaire,^{45 48} neuropathic pain-related DN4⁴⁸ and NPQ.⁴⁶

Quality assessment of included studies

Agreement was reached on 117 of 126 (93%) quality assessment items scored. Five studies^{43–46 48} were scored as having moderate RoB, resulting in fair overall quality. The remaining four studies^{42 47 49 50} were scored as having low RoB, resulting in good quality. Overall, the majority of the studies did not provide sample size justification or power description (criterion 5). Other two common sources of bias across the included studies were lack of blinded assessment (criterion 12) and analysis without including key potential confounders (criterion 14).

Table 2 Characteristics of included studies (n=9)

Study 1st author, year, country, design	Participants' characteristics	Marker(s) of inflammation	Experimental pain assessment	Statistical analysis	Quality
Arendt-Nielsen, ⁴² 2014, Denmark, CS	<p>Patients grouped according to experimental pain</p> <p>CPM, knee</p> <p>Most sensitised: n=42 (52% female); mean age 64.57±7.63 years; BMI=28.98±5.64 kg/m²; KL=1.95±0.94</p> <p>Medium sensitised: n=193 (30% female); mean age 67.71±3.66 years; BMI=27.46±3.93 kg/m²; KL=1.54±0.69</p> <p>Least sensitised: n=46 (30% female); mean age 63.40±7.32 years; BMI=27.68±4.03 kg/m²; KL=1.82±0.85</p> <p>TS, knee</p> <p>Most sensitised: n=46 (49% female); mean age 65.37±5.87 years; BMI=26.82±3.75 kg/m²; KL=1.77±0.72</p> <p>Medium sensitised: n=187 (55% female); mean age 65.80±7.28 years; BMI=28.20±4.64 kg/m²; KL=1.74±0.83</p> <p>Least sensitised: n=48 (37% female); mean age 63.37±7.95 years; BMI=30.14±4.78 kg/m²; KL=2.04±0.77</p> <p>OA definition: ACR</p> <p>Symptoms duration: N.R.</p> <p>OA duration: N.R.</p>	<p><u>Blood samples</u></p> <p>Serological markers: hsCRP</p>	<p>PPT (8 knee locations, muscle tibialis anterior, muscle extensor carpi radialis)</p> <p>TS (pressure pain)</p> <p>CPM</p>	<p>Repeated measures ANOVA and post-hoc test (t-test with Bonferroni correction)</p>	Good
Imamura, ⁴³ 2015, Brazil, CS	<p>OA group: n=53 (100% female); mean age 71.23±7.62 years; BMI=28.33±5.95 kg/m²</p> <p>OA definition: ACR, KL grade 2–4 and VAS >4 (averaged daily pain for the past month and lasting ≥3 months)</p> <p>Symptoms duration: at least 24 months; median 96 months (range 36–150)</p> <p>OA duration: N.R.</p>	<p><u>Blood samples</u></p> <p>Proinflammatory cytokines: IL-6, IL-8, TNF-α</p> <p>Anti-inflammatory cytokine: IL-10</p>	<p>PPT over vastus medialis, adductor longus, rectus femoris, vastus lateralis, tibialis anterior, peroneus longus, iliacus, sartorius, gracilis, quadratus lumborum and popliteus</p> <p>PPT over supraspinous ligaments (L1–L2, L2–L3, L3–L4, L4–L5, L5–S1, S1–S2)</p> <p>Hyperalgesia: pinch and roll manoeuvre at the L1, L2, L3, L4, L5, S1 and S2 dermatomes</p>	<p>Spearman correlation</p> <p>Mann-Whitney U</p>	Fair
Lee, ⁴⁴ 2011, USA, CS	<p>OA group: n=26 (76.9% female); mean age 59±7.5 years; BMI=27.5 (IQR: 24.8–32.6) kg/m²</p> <p>OA definition: clinically diagnosed knee OA, documented by a physician</p> <p>Symptoms duration: N.R.</p> <p>OA duration: N.R.</p> <p>Controls: n=33 (69.7% female); mean age 57.7±10.3 years; BMI=27.9 (IQR: 24.3–30.0) kg/m²</p>	<p><u>Blood samples</u></p> <p>CRP, IL-6, IL-1β, TNF-α</p>	<p>PPT at the trapezius, 1st metacarpophalangeal joint and quadriceps</p> <p>Heat pain threshold+suprathreshold heat pain ratings on ventral forearm</p> <p>Cold pressor task</p>	<p>General linear mixed models</p>	Fair
Li, ⁴⁵ 2020, China, CS	<p>n=83 (74.7% female); mean age 63.4±10.4 years; BMI=N.R.</p> <p>OA definition: ACR</p> <p>KL grade</p> <p>1: 20</p> <p>2: 48</p> <p>3: 12</p> <p>4: 3</p> <p>Symptoms duration: N.R.</p> <p>OA duration: N.R.</p>	<p><u>SF samples</u></p> <p>Inflammatory cytokines: IL-1β, IL-6, TNF-α</p>	<p>painDETECT</p>	<p>Spearman correlation</p>	Fair
Neogi, ⁵⁰ 2016, USA, cohort	<p>n=1111 with knee OA or at risk (62% female), mean age 66.9±7.5 years; BMI=29.7±4.8 kg/m²; 38% with radiographic knee OA</p> <p>Subjects free of TS at baseline</p> <p>n=716 (61% female); mean age 66.3±7.4 years; BMI=29.7±4.8; 37% with radiographic knee OA</p> <p>OA definition: sample from MOST Study</p> <p>KL grade 0–3 and frequent knee pain in the past 30 days or no frequent pain, but with at least one risk factor (history of knee injury/operation, overweight/obese)</p> <p>Symptoms duration: N.R.</p> <p>OA duration: N.R.</p>	<p><u>Non-CE-MRI</u></p> <p>Hoffa-synovitis (0–3) (WORMS)</p> <p>Effusion (0–3) (WORMS)</p> <p>BMLs (0–3) (WORMS)</p>	<p>PPT knee (peripheral sensitisation)</p> <p>PPT wrist (central sensitisation)</p> <p>TS mechanical (central sensitisation)</p>	<p>Linear regression</p> <p>Logistic regression</p> <p>Conditional logistic regression</p>	Good

Continued

Table 2 Continued

Study 1st author, year, country, design	Participants' characteristics	Marker(s) of inflammation	Experimental pain assessment	Statistical analysis	Quality
Petersen, ⁴⁹ 2016, Denmark, CC	<p>Patients with KOA</p> <p>BLOKS 0 n=16 (75% female), mean age 67.9±5.75 years; BMI=30.5±3.0 kg/m²; KL grade: 3.9 (95% CI: 3.7 to 4.0) OA duration: 11.5 years (95% CI: 4.2 to 18.8) Symptoms duration: N.R.</p> <p>BLOKS 1 n=24 (46% female), mean age 67.5±4.9 years; BMI=30.7±2.65 kg/m²; KL grade: 4 (95% CI: 4.0 to 4.0) OA duration: 13.5 years (95% CI: 8.8 to 18.1) Symptoms duration: N.R.</p> <p>BLOKS 2 and 3 n=21 (57% female), mean age 69.1±4.1 years; BMI=29.1±2.7 kg/m²; KL grade: 3.9 (95% CI: 3.7 to 4.0) OA duration: 15.3 years (95% CI: 10.0 to 20.6) Symptoms duration: N.R. OA definition: patients with KOA scheduled for TKA</p> <p>Controls VAS <10 mm, KL <2, no long-lasting pain problems in the past year n=33 (55% female), mean age 66.3±1.8 years; BMI=27.0±1.4 kg/m²</p>	<p><u>Non-CE-MRI</u> Degrees of synovitis: no (BLOKS 0), low (BLOKS 1), moderate (BLOKS 2) or severe (BLOKS 3)</p>	PPT (7 sites in the peripatellar region)	ANOVA	Fair
Radojčić, ⁴⁶ 2017, Denmark, CS	n=104 (62% female); mean age 66.78±7.24 years; BMI=30.4±5.21 kg/m ² OA definition: ACR (clinical and radiological); patients scheduled for TKA Symptoms duration: ≥6 months before enrolment OA duration: N.R.	<p><u>non-CE-MRI</u> Synovitis (MOAKS) Effusion/synovitis (MOAKS)</p> <p><u>CE-MRI</u> Synovitis (11-point score on CE images)</p> <p><u>Blood and SF</u> Plasma IL-6 SF IL-6</p>	NPQ	Spearman correlation Linear regression Logistic regression	Good
Sofat, ⁴⁷ 2019, UK, CS	<p>Patients with OA (n=120)</p> <p>Advanced OA n=78 (64% female); mean age 68.9±7.7 years; BMI=32.3±5.6 kg/m²</p> <p>Mild OA n=42 (71% female); mean age 64.1±9.6; BMI=29.2±4.7 kg/m² OA definition: ACR; KL grade ≥2 Symptoms duration: N.R. OA duration: N.R.</p>	<p><u>Non-CE-MRI</u> Synovitis (MOAKS) BML load (MOAKS)</p>	<p>PPT</p> <ul style="list-style-type: none"> ▶ 5 areas on the knee ▶ 5 areas on contralateral knee ▶ Lateral malleolus ▶ Right and left radius 	Pearson correlation	Good
Tchetina, ⁴⁸ 2020, Russia, CS	n=50 (74% female); mean age 67.6±7.5 years; BMI=30.5±9.05 kg/m ² KL 3: 37 4: 13 OA definition: ACR, KL Symptoms duration: permanent pain during the last 3 months before enrolment OA duration: 9.9 years (range 3–30)	<p><u>Blood samples</u> TNF-α, IL-1β gene expression</p>	DN4 painDETECT	Spearman correlation	Fair

ACR, American College of Rheumatology; ANOVA, analysis of variance; BLOKS, Boston-Leeds Osteoarthritis Knee Score; BMI, body mass index; BML, bone marrow lesion; CC, case-control; CE-MRI, contrast-enhanced MRI; CPM, conditioned pain modulation; CS, cross-sectional; DN4, Douleur Neuropathique-4 Questions; hsCRP, high-sensitivity C reactive protein; IL, interleukin; KL, Kellgren-Lawrence score; KOA, knee osteoarthritis; MOAKS, MRI Osteoarthritis Knee Score; NPQ, Neuropathic Pain Questionnaire; N.R., not reported; OA, osteoarthritis; PPT, pressure pain threshold; SF, synovial fluid; TKA, total knee arthroplasty; TNF-α, tumour necrosis factor-α; TS, temporal summation; VAS, Visual Analogue Scale; WOMRS, Whole Organ MRI Score.

Results of methodological quality assessment are outlined in [table 3](#).

Associations

Results on the associations between inflammatory signs and measures of altered pain perception mechanisms are

outlined in [table 4](#). An overview of the level of evidence and level of conclusion is reported in [table 5](#).

Effusion/synovitis and pain sensitivity

Three studies^{47 49 50} presented data on associations between effusion/synovitis and pain sensitivity. Although

Table 3 Quality assessment of included studies

Study 1st author, year	Study design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall RoB
Arendt-Nielsen, ⁴² 2014	CS	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	N	NA	Y	8/10=80% low
Imamura, ⁴³ 2015	CS	Y	Y	Y	N	N	NA	NA	Y	Y	NA	N	Y	NA	N	6/10=60% moderate
Lee, ⁴⁴ 2011	CS	Y	N	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	N	6/10=60% moderate
Li, ⁴⁵ 2020	CS	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	N	6/10=60% moderate
Neogi, ⁵⁰ 2016	C	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	12/14=86% low
Petersen, ⁴⁹ 2016	CC	Y	Y	Y	Y	N	Y	CD	Y	N	Y	Y	Y	/	/	9/12=75% moderate
Radojčić, ⁴⁶ 2017	CS	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	Y	8/10=80% low
Sofat, ⁴⁷ 2019	CS	N	Y	Y	Y	Y	NA	NA	Y	Y	NA	Y	Y	NA	Y	9/10=90% low
Tchetina, ⁴⁸ 2020	CS	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	NR	NA	N	7/10=70% moderate

<7 (50%)→<7 (50%)→high RoB=poor quality; 7-10 (50%-75%)→moderate RoB=fair quality; 11-14 (>75%)→low RoB=good quality.
 C, cohort; CC, case-control; CD, cannot determine; CS, cross-sectional; N, no; NA, not applicable; NR, not reported; RoB, risk of bias; Y, yes.

PPT was primarily used, the QST protocols differ significantly across studies (eg, different testing regions). Two studies revealed that patients with OA with MRI-detected presence of synovitis or effusion showed significantly lower PPT values at the knee when compared with those without^{49 50} or to those with lower grade of effusion or synovitis.⁴⁹ Further, a longitudinal cohort study reported that individuals with synovitis exhibit worsening PPT at the patella over time.⁵⁰ Moreover, presence of knee effusion resulted in an increased risk of developing TS at the patella and with a decrease in PPT at the wrist after 24 months.⁵⁰ In contrast, Sofat *et al* found no significant associations between structural signs of synovitis on non-contrast-enhanced MRI and PPT at the knee in those with mild to advanced knee OA.⁴⁷ According to conclusion level 2, inflammatory signs of effusion/synovitis may be associated with signs of pain sensitivity.

BMLs and pain sensitivity

According to conclusion level 2, the included studies could not establish an association between BMLs and pain sensitivity.^{47 50}

Inflammatory cytokines and pain sensitivity

There is conflicting evidence on the association between inflammatory cytokines and pain sensitivity (conclusion level 4). One study showed that serum levels of TNF- α were positively correlated with lower pressure tolerance at areas located further beyond the painful knee joint.⁴³ For other proinflammatory (IL-6 and IL-8) and anti-inflammatory (IL-10) cytokines, although heightened in patients with OA compared with controls, no correlation was found with PPT.⁴³ Another study reported that serum levels of IL-6 were significantly associated with cold pain tolerance and heat pain ratings (heightened pain sensitivity was associated with elevated IL-6).⁴⁴ IL-1 β and TNF- α were not significantly associated with any experimental pain measures.⁴⁴

According to conclusion level 3, two studies indicated a possible association between CRP levels and pain sensitivity.^{42 44} One study described a significant association between higher serum CRP levels and greater local/spreading pain sensitivity,⁴² and another study reported a significant association between serum CRP levels and PPT at multiple locations, indicating widespread hyperalgesia.⁴⁴

Effusion/synovitis and neuropathic-like pain

Limited evidence suggested a possible association between synovitis and neuropathic-like pain (conclusion level 4). Synovitis on contrast-enhanced MRI (measured by a composite score obtained summing synovial thickness measured in millimetres at 11 anatomical knee regions) showed a significant positive correlation with neuropathic-like pain (measured by NPQ) in patients undergoing total knee replacement surgery.⁴⁶ Other MRI findings including synovial volume, Hoffa-synovitis

Table 4 Associations between inflammatory signs and measures of altered pain perception mechanisms

Study	Associations	Results	Confounders	Level of evidence
Effusion/synovitis and pain sensitivity				
Petersen <i>et al</i> ⁴⁹	A significant BLOKS group effect in the ANOVA of the PPTs	Site 1 (ANOVA: $F_2=3.14$, $p<0.03$) Site 2 (ANOVA: $F_2=6.59$, $p<0.001$) Site 3 (ANOVA: $F_2=4.04$, $p<0.01$) Site 4 (ANOVA: $F_2=3.43$, $p<0.02$) Site 5 (ANOVA: $F_2=2.40$, $p<0.07$) Site 6 (ANOVA: $F_2=4.49$, $p<0.006$) Site 7 (ANOVA: $F_2=1.24$, $p<0.3$)	BMI, sex and age	B
Neogi <i>et al</i> ⁶⁰	Hoffa-synovitis (baseline)—PPT patella (baseline)	$\beta=-0.42$ (95% CI: -0.67 to -0.18)	Age, sex, BMI, race, study site, KL, presence of patellofemoral OA, depressive symptoms, catastrophising, widespread pain, use of analgesics	A2
	Hoffa-synovitis (baseline)—PPT patella change (follow-up 24 months)	$\beta=-0.30$ (95% CI: -0.52 to -0.08)		
	Hoffa-synovitis (baseline)—PPT wrist (baseline)	$\beta=-0.19$ (95% CI: -0.35 to -0.03)		
	Hoffa-synovitis (baseline)—PPT wrist change (follow-up 24 months)	$\beta=-0.10$ (95% CI: -0.26 to 0.06)		
	Effusion (baseline)—PPT patella (baseline)	$\beta=0.23$ (95% CI: -0.03 to 0.49)		
	Effusion (baseline)—change PPT patella (follow-up 24 months)	$\beta=-0.04$ (95% CI: -0.28 to 0.19)		
	Effusion (baseline)—PPT wrist (baseline)	$\beta=-0.24$ (95% CI: -0.40 to -0.07)		
	Effusion (baseline)—PPT wrist change (follow-up 24 months)	$\beta=-0.24$ (95% CI: -0.41 to -0.08)		
	Hoffa-synovitis (baseline)—TS patella (baseline) (n=1111)	OR=0.83 (95% CI: 0.63 to 1.08)		
	Hoffa-synovitis (baseline)—TS patella incident (n=716)	OR=1.12 (95% CI: 0.75 to 1.66)		
	Hoffa-synovitis (baseline)—TS wrist (baseline) (n=1111)	OR=0.84 (95% CI: 0.75 to 1.66)		
	Hoffa-synovitis (baseline)—TS wrist incident (n=716)	OR=1.22 (95% CI: 0.85 to 1.75)		
	Effusion (baseline)—TS patella (baseline) (n=1111)	OR=0.89 (95% CI: 0.67 to 1.18)		
	Effusion (baseline)—TS patella incident (n=716)	OR=1.54 (95% CI: 1.01 to 2.36)		
Effusion (baseline)—TS wrist (baseline) (n=1111)	OR=1.13 (95% CI: 0.85 to 1.51)			
Effusion (baseline)—TS wrist incident (n=716)	OR=0.94 (95% CI: 0.66 to 1.35)			
Sofat <i>et al</i> ⁴⁷	Synovitis—PPT	$r=-0.02$, N.S.	N.A.	C
BMLs and pain sensitivity				
Neogi <i>et al</i> ⁶⁰	BMLs—PPT patella (baseline)	$\beta=0.14$ (95% CI: -0.16 to 0.08)	Age, sex, BMI, race, study site, KL, presence of patellofemoral OA, depressive symptoms, catastrophising, widespread pain, use of analgesics	A2
	BMLs—change PPT patella (follow-up 24 months)	$\beta=0.03$ (95% CI: -0.25 to 0.31)		
	BMLs—PPT wrist (baseline)	$\beta=0.05$ (95% CI: -0.14 to 0.25)		
	BMLs—PPT wrist change (follow-up 24 months)	$\beta=-0.10$ (95% CI: 0.29 to 0.10)		
	BMLs sum—PPT patella (baseline)	$\beta=0.03$ (95% CI: -0.01 to 0.08)		
	BMLs sum—change PPT patella (follow-up 24 months)	$\beta=-0.01$ (95% CI: -0.05 to 0.04)		
	BMLs sum—PPT wrist (baseline)	$\beta=0.00$ (95% CI: -0.03 to 0.03)		
	BMLs sum—PPT wrist change (follow-up 24 months)	$\beta=0.00$ (95% CI: -0.03 to 0.03)		
	BMLs—TS patella (baseline) (n=1111)	OR=0.95 (95% CI: 0.68 to 1.32)		
	BMLs—TS patella incident (n=716)	OR=0.92 (95% CI: 0.56 to 1.49)		
	BMLs—TS wrist (baseline) (n=1111)	OR=1.04 (95% CI: 0.74 to 1.45)		
	BMLs—TS wrist incident (n=716)	OR=1.05 (95% CI: 0.68 to 1.62)		
	BMLs sum—TS patella (baseline) (n=1111)	OR=0.98 (95% CI: 0.93 to 1.03)		
	BMLs sum—TS patella incident (n=716)	OR=1.00 (95% CI: 0.92 to 1.07)		
	BMLs sum—TS wrist (baseline) (n=1111)	OR=0.98 (95% CI: 0.93 to 1.04)		
	BMLs sum—TS wrist incident (n=716)	OR=1.00 (95% CI: 0.94 to 1.07)		
Sofat <i>et al</i> ⁴⁷	BML_load—PPT	$r=-0.069$, N.S.	N.A.	C
	nBML—PPT	$r=-0.114$, N.S.		
Inflammatory cytokines and pain sensitivity				
Imamura <i>et al</i> ⁴³	IL-6—PPT	N.S.	/	C
	IL-10—PPT	N.S.		
	TNF- α —PPT	Significantly associated with the majority of PPT measures of the muscular, ligamentous or subcutaneous sources ($p<0.05$)		

Continued

Table 4 Continued

Study	Associations	Results	Confounders	Level of evidence
Lee <i>et al</i> ⁴⁴	Log IL-6—PPT quadriceps	F=0.98, p=N.S.	BMI	C
	Log IL-6—(PPT quadriceps) ²	N.S.		
	Log IL-6—PPT thumb	F=0.02, N.S.		
	Log IL-6—(PPT thumb) ²	N.S.		
	Log IL-6—PPT trapezius	F=0.97, N.S.		
	Log IL-6—(PPT trapezius) ²	N.S.		
	Log IL-6—HPT	F=0.27, N.S.		
	Log IL-6—HPR at 49°C	F=4.51, p=0.04		
	Log IL-6—(HPR at 49°C) ²	F=4.27, p=0.05		
	Log IL-6—HPR at 51°C	F=5.79, p=0.02		
	Log IL-6—(HPR at 51°C) ²	F=5.26, p=0.03		
	Log IL-6—CPR	F=0.03, p=N.S.		
	Log IL-6—CPR ²	N.S.		
	Log IL-6—CPT	F=5.96, p=0.02		
	Log IL-6—CPT ²	F=6.57, p=0.02		
	IL-1β—pain measures	N.S., data N.R.		
	TNF-α—pain measures	N.S., data N.R.		
C reactive protein and pain sensitivity				
Arendt-Nielsen <i>et al</i> ⁴²	hsCRP—local/spreading sensitisation/TS	Association sign, data N.R.	Unadjusted	B
Lee <i>et al</i> ⁴⁴	Log CRP—PPT quadriceps	F=8.13, p=0.009	Unadjusted	C
	Log CRP—(PPT quadriceps) ²	F=6.58, p=0.02		
	Log CRP—PPT thumb	F=7.44, p=0.01		
	Log CRP—(PPT thumb) ²	N.S.		
	Log CRP—PPT trapezius	F=9.99, p=0.004		
	Log CRP—(PPT trapezius) ²	F=9.36, p=0.006		
	Log CRP—HPT	F=0.55, p=N.S.		
	Log CRP—HPR at 49°C	F=1.17, N.S.		
	Log CRP—(HPR at 49°C) ²	N.S.		
	Log CRP—HPR at 51°C	F=1.96, N.S.		
	Log CRP—(HPR at 51°C) ²	N.S.		
	Log CRP—CPR	F=5.20, p=0.03		
	Log CRP—CPR ²	F=5.11, p=0.03		
	Log CRP—CPT	F=0.74, N.S.		
	Log CRP—CPT ²	N.S.		
Effusion/synovitis and neuropathic-like pain				
Radojčić <i>et al</i> ⁴⁶	11-point synovitis—NPQ	r=0.25, p=0.011	BMI, sex and age	C
Inflammatory cytokines and neuropathic-like pain				
Li <i>et al</i> ⁴⁵	IL-1β—painDETECT	r=−0.019, N.S.	N.A.	C
	IL-6—painDETECT	r=−0.034, N.S.		
	TNF-α—painDETECT	r=−0.115, N.S.		
Radojčić <i>et al</i> ⁴⁶	Plasma IL-6—NPQ	β=4.029 (95% CI: −0.032 to 0.838)	BMI, sex and age	C
	Synovial fluid IL-6—NPQ	β=0.043 (95% CI: 0.005 to 0.082)		
Tchetina <i>et al</i> ⁴⁸	TNF-α—DN4	r=0.330, p=0.02	N.A.	C
	IL-1β—DN4	r=0.496, p<0.01		
	IL-1β—painDETECT	r=0.313, p=0.04		

ANOVA, analysis of variance; BLOKS, Boston-Leeds Osteoarthritis Knee Score; BMI, body mass index; BMLs, bone marrow lesions; CPR, cold pain rating; CPT, cold pain tolerance; DN4, Douleur Neuropathique-4 Questions; HPR, heat pain rating; HPT, heat pain threshold; (hs)CRP, (high-sensitivity) C reactive protein; IL, interleukin; KL, Kellgren-Lawrence score; N.A., not applicable; NPQ, Neuropathic Pain Questionnaire; N.S., not significant; OA, osteoarthritis; PPT, pressure pain threshold; TNF-α, tumour necrosis factor-α; TS, temporal summation.

Table 5 Level of conclusion for associations between inflammatory signs and altered pain perception (pain sensitivity and neuropathic-like pain)

Associations	Level of evidence					Level of conclusion
	A1	A2	B	C	D	
Inflammatory signs—pain sensitivity						
Effusion/synovitis		Neogi <i>et al</i> ⁵⁰ [+]	Petersen <i>et al</i> ⁴⁹ [+]	Sofat <i>et al</i> ⁴⁷ [ns]		2
BMLs		Neogi <i>et al</i> ⁵⁰ [ns]		Sofat <i>et al</i> ⁴⁷ [ns]		2
Pro-inflammatory cytokines						4
IL-1 β				Lee <i>et al</i> ⁴⁴ [ns]		
IL-6				Imamura <i>et al</i> ⁴³ [ns] Lee <i>et al</i> ⁴⁴ [+]		
TNF- α				Imamura <i>et al</i> ⁴³ [ns] Lee <i>et al</i> ⁴⁴ [+]		
CRP			Arendt-Nielsen <i>et al</i> ⁴² [+]	Lee <i>et al</i> ⁴⁴ [+]		3
Inflammatory signs—neuropathic-like pain						
Effusion/synovitis				Radojčić <i>et al</i> ⁴⁶ [+]		4
Pro-inflammatory cytokines						4
IL-1 β				Li <i>et al</i> ⁴⁵ [ns] Tchetina <i>et al</i> ⁴⁸ [+]		
IL-6				Li <i>et al</i> ⁴⁵ [ns] Radojčić <i>et al</i> ⁴⁶ [ns]		
TNF- α				Li <i>et al</i> ⁴⁵ [ns] Tchetina <i>et al</i> ⁴⁸ [+]		

Level of evidence: A1=systematic reviews and meta-analyses, based on minimally two independent A2 studies; A2=prospective cohort studies with sufficient sample size and follow-up; adequately controlled for confounding factors and precluding selective loss to follow-up; B=prospective cohort studies, but lacking the quality criteria of A2; retrospective cohort studies and case-control studies; C=non-comparative studies; D=expert opinion. [+]Significant positive association. [ns]Not significant association. [-]Significant negative association. Level of conclusion: 1=one A1 or at least two independent A2 studies that support each other's conclusions and do not show conflicting evidence; 2=one A2 or at least two independent B studies that support each other's conclusions and do not show conflicting evidence; 3=one B or at least two C studies that support each other's conclusions and do not show conflicting evidence; 4=research at level C or two or more independent studies at higher level that do not support each other's conclusions and hence, show conflicting evidence; consensus=there is no evidence, but consensus (level D); no conclusions=there is no evidence and no consensus.

BMLs, bone marrow lesions; CRP, C reactive protein; IL, interleukin; TNF- α , tumour necrosis factor- α .

and whole-knee effusion were not significantly correlated with NPQ score.⁴⁶

Inflammatory cytokines and neuropathic-like pain

No association was found between inflammatory cytokines and painDETECT score.⁴⁵ The NPQ and IL-6 levels in synovial fluid, but not in plasma, were significantly correlated.⁴⁶ In patients with end-stage OA, higher neuropathic-like pain scores on painDETECT and DN4 Questionnaires were found to be positively correlated with gene expression of TNF- α and IL-1 β .⁴⁸ Taking these results together, there is conflicting evidence on a

possible association between inflammatory cytokines and neuropathic-like pain (conclusion level 4).

DISCUSSION

The aim of this systematic review was to synthesise and evaluate the available literature on the associations between knee inflammation (as measured by effusion, synovitis, BMLs and cytokines) and altered pain processing (assessed by QST and/or questionnaires for neuropathic-like pain) in patients with knee OA.

The main findings indicate a probable positive association between knee inflammation and altered pain

processing (pain sensitivity and neuropathic-like pain). Specifically, local inflammatory signs of effusion and synovitis assessed by non-contrast MRI were found to be positively associated with altered pain sensitivity (measured by PPT and TS). Synovitis measured on contrast-enhanced MRI was found to be positively associated with presence of neuropathic-like pain. However, this finding is based on one study only. At a systemic level, conflicting evidence was found on the association between serum levels of inflammatory cytokines (IL-1 β , IL-6 and TNF- α) and pain sensitivity. Serum CRP levels, a measure of systemic inflammation, were found to be positively associated with lower PPT and presence of TS. However, the limited amount of included articles, most of which (56%) have moderate RoB along with some conflicting evidence, makes it difficult to draw strong conclusions and indicates the need for further research on these associations.

From our results, it emerges that knee local inflammatory lesions such as synovitis and effusion may be positively associated with pain sensitivity (conclusion level 2). Synovitis in knee OA is characterised by hyperplasia of synovial fibroblasts, which are a major source of proinflammatory cytokines⁵¹ that can sensitise nociceptors.⁵² Included studies of moderate to good quality suggest a positive association between signs of synovitis (effusion/synovitis measured on non-contrast-enhanced MRI) and hyperalgesia expressed by lower PPT (at the knee and at a remote site from the affected knee). Neogi *et al* showed that individuals with synovitis demonstrate a lower PPT at the knee and a decrease of this threshold over 2 years, reflecting an increased pain sensitivity in those participants.⁵⁰ Effusion at baseline was associated with a higher risk of developing TS (an augmented response to repetitive equal-intensity noxious stimuli) and with a decrease in PPT at the wrist after 24 months.⁵⁰ These results support the notion that in the course of joint inflammation, nociceptors experience increased stimulation and that persistent activation can contribute to the development of central sensitisation.³³ This has also been demonstrated in rodent models of OA pain, in which synovitis is followed by evidence of central sensitisation.⁵³ Therefore, effusion and synovitis are two attractive therapeutic targets for interventions aiming to prevent the occurrence of sensitisation which, in turn, may prevent pain to become chronic and more severe.

Recently, there has been a growing interest in the role of subchondral bone in OA pain. BMLs are considered to be (micro)traumatic lesions related to excessive mechanical load or remodelling related to tissue injury.⁵⁴ In OA, BML changes may contribute to pain also due to a proinflammatory environment in which angiogenesis, along with new sensory nerves, occurs.⁵⁵ However, the studies included in this review did not find an association between BMLs measured by non-contrast MRI and signs of pain sensitivity (conclusion level 2). This could be due to the limited amount of information as only two of the included studies investigated these possible

associations.^{47 50} Furthermore, heterogeneity of included patients in both studies was high. Recent evidence based on animal models showed that pain induced by acute inflammatory response in early monoiodoacetate (MIA)-induced OA involves sensitisation of nerves innervating the joint capsule but not the underlying subchondral bone, while pain in late MIA-induced OA involves the additional recruitment of nerves that innervate the subchondral bone.⁵⁶ These findings suggest that the role of BMLs in pain generation may differ according to the OA severity. However, the two included studies reporting data on the association between BMLs and pain sensitivity included patients with high heterogeneity ranging from early to late knee OA.^{47 50} This could be an additional reason for which an association between BMLs and pain sensitivity was not found.

At a molecular level, proinflammatory cytokines have been considered to play important roles in knee OA pain.⁵⁷ In case of synovitis, the synovial membrane becomes hyperplastic and infiltrated with immune cells with subsequently increased levels of proinflammatory mediators in peripheral blood and synovial fluid.^{58 59} Proinflammatory cytokines such as IL-1 β , IL-6 and TNF- α can directly activate nociceptive sensory neurons and contribute to sensitisation.^{26 33} Our results showed conflicting evidence regarding a possible significant association between cytokines and pain sensitivity (conclusion level 4). TNF- α was associated with lower PPTs at multiple anatomical regions. This suggests that higher serum levels of TNF- α may be linked to both local as well as widespread hyperalgesia. These results are congruent with experimental animal studies in which TNF- α could induce sensitisation.^{60 61} Similarly, in animal models, it was shown that a single injection of either IL-6 or IL-1 β induced mechanical peripheral sensitisation.^{62 63} In the included studies, serum concentrations of IL-6 and IL-1 β were not associated with pain sensitivity. Degradation of cartilage fragments causes production of inflammatory mediators in synovial cells, of which CRP is most discussed and considered to be an indicator of an acute inflammatory state.³⁰ According to the results of two studies included in this review, there may be an association between CRP levels and pain sensitivity (TS and widespread hyperalgesia) (conclusion level 3). Patients with OA with elevated CRP levels experience lower pain thresholds on local and distant locations and less tolerance to cold-induced pain.

Apart from pain sensitivity, altered pain mechanisms in OA can be reflected by signs of neuropathic-like pain features.¹³ Inflammatory processes within the joint can cause continuous stimulation of nociceptors with subsequent sensitisation. Knee OA is characterised by chronic and low-grade inflammation⁶⁴ in which nociceptors might be continuously stimulated with possible subsequent sensitisation and possibly the development of neuropathic-like pain.^{65–67} In our results, one cross-sectional study showed an association between local knee inflammation (synovitis) and neuropathic-like

pain⁴⁶ (conclusion level 4). No clear evidence was found regarding systemic inflammatory signs (cytokines) and their association with presence of neuropathic-like pain (conclusion level 4). Only one study reported consistent significant results on blood levels of proinflammatory cytokines which were found to be correlated with presence of neuropathic-like pain, but the correlation values did not go beyond the moderate level (ie, r values ≤ 0.5).⁴⁸ However, the study sample included only patients with advanced knee OA and the analyses did not include potential confounders.⁴⁸ Importantly, the results of Radojčić *et al* revealed that the association between synovial fluid IL-6 and neuropathic-like pain was explained by synovitis.⁴⁶ However, further research is needed to strengthen the evidence. In addition to proinflammatory cytokines, biomarkers of extracellular matrix turnover (such as matrix metalloproteinases (MMPs) and derived degradation products of type I–II and III collagen) are also implicated in OA inflammation.³⁰ One of the included studies measured serum levels of biomarkers of extracellular matrix turnover (CIM) and reported a positive significant association with neuropathic-like pain ($\beta=0.229$; 95% CI 0.036 to 0.422) depending on synovitis.⁴⁶ This finding further supports the possibility of an association between inflammation and neuropathic-like pain. However, another study measured synovial fluid levels of MMP-3 and MMP-13 and found no correlation with neuropathic-like pain.⁴⁵ These results were not included in the best-level synthesis as this review focused on proinflammatory cytokines which can directly trigger an increase in MMP synthesis⁶⁸ as well as contribute to sensitisation of joint nociceptors.²⁶

Our results need to be interpreted with caution as the included studies showed limitations. Statistical analyses varied widely between studies and most of these lack in inclusion of confounders. For example, out of three included studies presenting associations of data between inflammation and neuropathic-like pain, only one included potential confounders.⁴⁶ Age, sex, gender, BMI, pain severity, depressive symptoms, pain catastrophising and use of antidepressants are important confounders to consider when investigating possible associations with neuropathic-like pain.^{69–71} In addition, only three (33%) of the included studies reported information on duration of symptoms. This is a limit as long history of symptoms may be associated with presence of sensitisation or neuropathic-like pain.⁷² Furthermore, the majority of the included studies measured biomarker levels in serum while, in line with the results of the current review, it has been proposed that local biomarkers (in synovial fluid) may be more promising to show the association with pain and pain mechanisms.⁷³ The two studies investigating associations between cytokines and pain sensitivity have important limitations. The study of Imamura *et al* included only female participants, thus the results have limited generalisability.⁴³ The study of Lee *et al* had a small sample size ($n=26$) with a majority of female participants (77%) and lack of covariates.⁴⁴ Future studies

are encouraged to measure biomarkers both in serum and synovial fluid. Moreover, nociceptive, nociplastic and neuropathic-like pain may occur in combination in some patients, making it challenging to differentiate the exact underlying pain mechanism.²² For example, results from screening questionnaires to measure neuropathic-like pain may be confounded by the concurrent presence and severity of nociceptive and/or nociplastic pain within the same subject.^{22 72 74 75} Thus, it is difficult to establish a clear association between markers of inflammation and specific altered pain mechanisms. Lastly, included studies had a cross-sectional design; therefore, no cause–effect relationship could be established. Future studies can strengthen the level of evidence by applying a longitudinal design with adequate sample size and are encouraged to implement appropriate confounders in the analyses.

This systematic review comprises strengths and limitations. We performed a systematic literature search on four major databases without any restriction on the publication date. We provided an extensive summary of the literature by including articles involving patients with knee OA diagnosed with different accepted criteria and investigated for inflammatory signs and altered pain perception with different methodologies. However, this approach has the disadvantage of increasing heterogeneity. In fact, due to the heterogeneity of the patients' characteristics and outcome variables, we refrained from performing a meta-analysis. Lack of consistency across QST protocols remains a challenge within the field of OA.²⁵ Because of different protocols of pain testing and a variety of inflammatory markers being used, combining and summarising data for developing an overview of current literature were challenging. However, we carefully evaluated the methodological quality of the included papers and performed the best level of evidence that takes into account both study design and RoB. Furthermore, due to the limited amount of included studies in each level of the best evidence synthesis, formal methods to assess potential publication bias (eg, funnel plots inspection) could not be performed. Lastly, including articles that assessed pain sensitivity by relying solely on QST had the drawback of excluding studies that investigated altered pain perception mechanisms using different methodologies. Alternative techniques, such as brain imaging (eg, functional MRI) or self-reported questionnaires (eg, central sensitisation inventory) may provide additional insights.

CONCLUSIONS

Local inflammatory signs of effusion/synovitis may be positively associated with neuropathic-like pain and signs of pain sensitivity. Included studies revealed a possible positive association between serum CRP levels and pain sensitivity. However, these results need to be interpreted with caution due to the limited amount of included studies along with the high heterogeneity in different methodologies. The associations between inflammatory

signs and altered pain perception in patients with knee OA need to be explored further. Future high-quality studies with adequate sample size and long-term follow-up are needed to strengthen the level of evidence.

Contributors PD was the primary person responsible for designing and conducting the study. PD and HM drafted the PROSPERO protocol and performed the systematic literature search. PC acted as the third reviewer to resolve conflicts. PD and HM extracted the data, and performed the descriptive analyses, the risk of bias assessment and the best evidence synthesis. PD drafted the article. All authors revised the manuscript critically for content. PD, JS and PC are the guarantors of this work and, as such, had full access to all study data and take responsibility for the integrity of the data and accuracy of the data analysis. All authors read and approved the final manuscript.

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