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REVIEW

Understanding pain heterogeneity in osteoarthritis patients: a narrative review

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Abstract **The primary clinical manifestation of osteoarthritis (OA) is pain, yet considerable variability exists in the pain experience among OA patients. This narrative review aims to explore the mechanisms driving OA pain heterogeneity to inform the development of targeted interventions that improve treatment efficacy and patient outcomes. A comprehensive literature search was conducted across multiple databases (PubMed, Scopus, and Google Scholar) for papers published between January 1, 2020, and December 31, 2024. Inclusion criteria focused on studies addressing pain mechanisms and therapeutic interventions in OA. This review identifies key mechanisms of OA pain, including joint alterations, angiogenesis, nervous system involvement, peripheral and central sensitization, and psychosocial factors. It highlights the underlying distinct mechanisms in OA pain, which contribute to the variability in individuals' responses to treatment. It was suggested that interactions between neuroimmune and neurovascular systems are key contributors to chronic pain in OA. This narrative review emphasizes the complexity of OA pain, highlighting the importance of thoroughly understanding the underlying mechanisms for developing personalized and effective pain management strategies. Additional research is required to refine treatment approaches and explore long-term effects.**

Keywords osteoarthritis; pain; structural alteration; nervous system; psychosocial factors; therapeutics

Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease that leads to pain, stiffness, swelling, and limited joint mobility [1]. It has risen to the leading cause of global burden with an upward trend over the past two decades, especially among people over 50 years [2,3]. The predominant manifestation of OA is pain, which increases in frequency and intensity as the disease advances and serves as the main impetus for seeking medical attention [1]. Articular cartilage degradation, subchondral bone remodeling, synovial hyperplasia, and osteophyte formation are hallmarks of OA [4]. Synovial inflammation and bone marrow edema were the primary structural changes strongly associated with the development of pain [5]. Nevertheless, 30%–40% of individuals suffering from the most severe types of radiographic OA do not experience pain, which means the extent of radiographic changes in OA does not precisely align with pain intensity [6]. Gaining insights into the underlying pathological mechanisms of OA pain is crucial for developing personalized and more effective pain-relieving treatments.

The widespread acceptance of the definition of pain refers to an unpleasant sensory and emotional experience linked to or like the experience of actual or potential harm to body tissues [7]. OA pain has traditionally been categorized as nociceptive, originating from tissue damage or inflammation in the joints, and is characterized by localized pain that worsens with movement and weight-bearing activities [8]. However, recent research has highlighted the contribution of neuropathic and

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nociplastic pain mechanisms to OA pain. Neuropathic pain involving nerve damage presents with distinct somatosensory symptoms, including burning sensations, paresthesia, tingling, mechanical and thermal hyperalgesia, allodynia, paroxysmal pain, and numbness [9]. On the other hand, nociplastic pain is a term proposed by the global community of pain researchers to define a distinct category of pain that differs mechanistically from nociceptive pain, which results from tissue inflammation and damage, and neuropathic pain, which arises from nerve damage [10]. This condition involves both peripheral and central pain sensitization, leading to heightened sensitivity to both painful and non-painful stimuli, and is often accompanied by fatigue, sleep disturbances, cognitive issues, hypersensitivity to environmental stimuli, and increased anxiety and depression [10]. Nociplastic pain can manifest independently or coexist with chronic pain conditions that are predominantly nociceptive or neuropathic. Recognizing this type of pain is crucial, as it responds differently to treatment than nociceptive pain, showing reduced effectiveness with peripherally targeted therapies such as anti-inflammatory drugs, opioids, surgery, or injections. Incorporating psycho-education on pain mechanisms and the impact of thoughts on sustaining pain was essential [11].

Most OA researchers have focused on analyzing the anatomy of the joints and the localized deterioration, regarding pain as a mere manifestation of joint destruction. In contrast, OA pain is a separate condition characterized by intricate underlying mechanisms, including inflammation affecting all parts of the joints and peripheral and central nervous system abnormalities. Mechanical or chemical stimuli activate the nociceptors of the afferent neurons in the joint, leading to receptor depolarization and pain transmission [12]. While inflammation and joint injury initially generate pain, prolonged exposure to harmful stimuli can lead to neural plasticity and an aberrant pain experience that is unrelated to the inflammation [12]. The phenomenon of amplified pain processing or reduced pain inhibition in the nervous system results in a final shared pathway that intensifies the perception, conversion, and transmission of pain signals [10]. The neuro-immune interaction in the joint microenvironment modulates pain perception, releasing neuropeptides and cytokines that can amplify nociceptive signaling. Angiogenesis and reinnervation of the local joint (synovium, menisci, osteochondral region, and ligaments) were also reported to be associated with OA pathogenesis and pain [13].

The mechanisms underlying pain perception differences in OA remain unknown, and the pathological severity of the joint is inconsistent with pain intensity. The interaction of peripheral and central sensitization with psychosocial factors complicates pain generation in OA. It has also been suggested that race and gender, in particular, may significantly impact the experience and effects of OA [14]. So far, nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics cannot provide satisfactory pain relief, with non-negligible side effects and utilization limits. Classifying OA pain into a single mechanistic category is an oversimplification, as many, if not most, pain conditions exhibit a mixed pain profile with significant mechanistic overlap. A thorough comprehension of the pathogenesis and sustaining aspects of OA pain might help identify individuals who would benefit from targeted therapy in alleviating symptoms and enhancing their ability to do everyday activities. This review aims to provide an update on OA pain sensation mechanisms and new insights for future OA pain research.

Materials and methods

A systematic literature search was conducted to examine the characteristics and mechanisms of OA pain. Relevant original research articles and review papers were identified through PubMed, Scopus, and Google Scholar between January 1, 2020, and December 31, 2024. The search included the following keywords: “osteoarthritis,” “pain,” “structural change,” “reinnervation,” “nerve growth factor,” “angiogenesis,” and “psychological factors.” Additionally, specific search queries such as (osteoarthritis AND pain), (osteoarthritis AND cartilage), (osteoarthritis AND synovial inflammation), (osteoarthritis AND subchondral bone), (osteoarthritis AND reinnervation), (osteoarthritis AND angiogenesis), and (osteoarthritis AND psychology) were applied.

Inclusion criteria: (1) studies investigating pain variability in OA based on biological, psychological, or social factors; (2) animal models used for OA pain studies and the results of emerging preclinical studies; (3) original articles and reviews published in English and between January 1, 2020, and December 31, 2024. Exclusion criteria: (1) editorials, case reports, and conference abstract; (2) non-English publications; (3) non-peer-reviewed publications; (4) duplicate and irrelevant records.

Overview of the classification in OA pain

In the initial phases of OA, pain often occurs sporadically but later becomes constant and intense as the illness advances, accompanied by considerable emotional discomfort and hampers daily activities [15]. Acute OA pain is primarily characterized by nociceptive pain arising from joint inflammation, cartilage degeneration, and mechanical stress [8]. It is often compounded by inflammatory pain due to synovitis and joint effusion. NSAIDs are the first-line pharmacologic treatment for

managing pain in osteoarthritis (OA) [16]. Unlike acute OA pain, which is intense and episodic, chronic OA pain is persistent, often involving multiple pain mechanisms, and leads to functional impairment and heightened pain sensitivity. The classification of chronic OA pain based on its predominant nociceptive, neuropathic, or nociplastic mechanisms is of significant clinical importance [17]. Neuropathic and nociplastic pain generally have limited responses to NSAIDs, as their underlying mechanisms —nerve damage and central sensitization—are not primarily driven by inflammation [10]. Tricyclic antidepressants and gabapentinoids are effective exclusively in the treatment of neuropathic pain [9]. Pharmaceutical treatments for nociplastic pain include antidepressants (e.g., duloxetine), anticonvulsants (e.g., gabapentinoids), and opioids, while non-pharmaceutical approaches encompass cognitive-behavioral therapy, physical therapy, and mindfulness-based interventions [10]. It is crucial to delineate the etiological, physiologic, and clinical distinctions between nociceptive, neuropathic, and nociplastic pain to facilitate accurate diagnosis and effective treatment of OA pain, as outlined below (Table 1).

Nociceptive pain

Nociceptive pain originates from activating peripheral nociceptors of afferent nerves in response to various stimuli, including mechanical, chemical, or thermal factors. Noxious stimuli act on the pain nociceptors in the sensory nerve endings of the OA joint, which generate signals that travel upward to the sensory center, resulting in the awareness of pain (Fig. 1).

OA pain is considered to be mechanically induced, resulting from the stimulation of nociceptive nerve fibers triggered by pathological changes in the afflicted joint [19]. Various types of molecules participate in sensitizing local sensory nerves in OA, comprising cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), neurotrophins like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), neuropeptides like substance P (SP) and calcitonin gene-related peptide (CGRP), as well as protons [20].

NGF is a pivotal cytokine mediating pain signal transduction, and its expression is increased in synovium and subchondral bone in OA patients [21]. NGF is synthesized by immune cells, such as macrophages, and promotes the transmission of pain signals via sensory neurons [22]. NGF generates pain sensation by binding to tropomyosin receptor kinase A (TrkA) [23]. The NGF-TrkA binding can initiate a signal transduction pathway that activates the transient receptor potential vanilloid 1(TRPV1), leading to pain sensation [24]. The NGF-TrkA-TRPV1 pathway was involved in neurogenic inflammation [23]. It was suggested that NGF-mediated ingrowth of TrkA-expressing axons drives abnormal osteochondral differentiation, and inhibiting NGF-TrkA signaling could serve a dual therapeutic purpose, acting both as an analgesic and as a negative regulator of aberrant stem cell differentiation [25]. It was reported that macrophages can modulate the threshold for pain sensitivity by producing NGF, and therefore, macrophage-neuron signaling is crucial for pain sensation and transmission in inflammatory or neuropathic conditions [22].

TRPV1 is a transduction channel abundant in nociceptive fibers (pain fibers) throughout the peripheral nervous system [26]. TRPV1 is crucial in the development of pain and neurogenic inflammation, and it is susceptible to activation by different triggers, such as vanilloid, noxious heat, endocannabinoids, membrane depolarization, extracellular protons, and inflammatory mediators [27]. In OA patients, TRPV1 expression and M1 macrophage infiltration were simultaneously increased in the synovium [28]. It was suggested that TRPV1 could slow the progression of OA and alleviate pain by inhibiting M1 macrophage polarization [28]. Capsaicin, a TRPV1 agonist, has demonstrated a remarkable therapeutic effect via ablation of the sensory fiber terminals, inhibiting all potential means of activating that pain fiber [29]. The efficacy of intra-articular trans-capsaicin was confirmed for OA pain management, with rapid improvement in walking-induced pain and few side effects [30]. A meta-analysis indicated that topical capsaicin may reduce pain severity but may also increase the burning sensation at the application site compared to a placebo [31]. TRPV1 may be a disease-modifying target for treating various OA pathologies due to its anti-pain, anti-inflammation, and anti-ferroptosis effects [32]. TRPV1 monoclonal antibody-coupled

Table 1 Classification of osteoarthritis (OA) pain

Type of pain	Etiology	Pathophysiological mechanisms	Clinical features
Nociceptive	Joint degeneration and inflammation	Activation of peripheral nociceptors due to tissue injury and inflammation	Localized, aching, sharp pain often triggered by movement or weight-bearing [8]
Neuropathic	Nerve damage from OA-related structural changes	Nerve compression or injury, abnormal nerve firing, and ectopic discharge	Burning, tingling, shooting, or electrical-like pain; may radiate [9]
Nociplastic	Dysfunction pain processing at the peripheral nociceptor, spinal cord, or brain level	Peripheral and central sensitization-enhanced pain signaling and decreased inhibition pathways	Diffuse, aching, or deep pain that may be disproportionate to observable tissue damage [18]

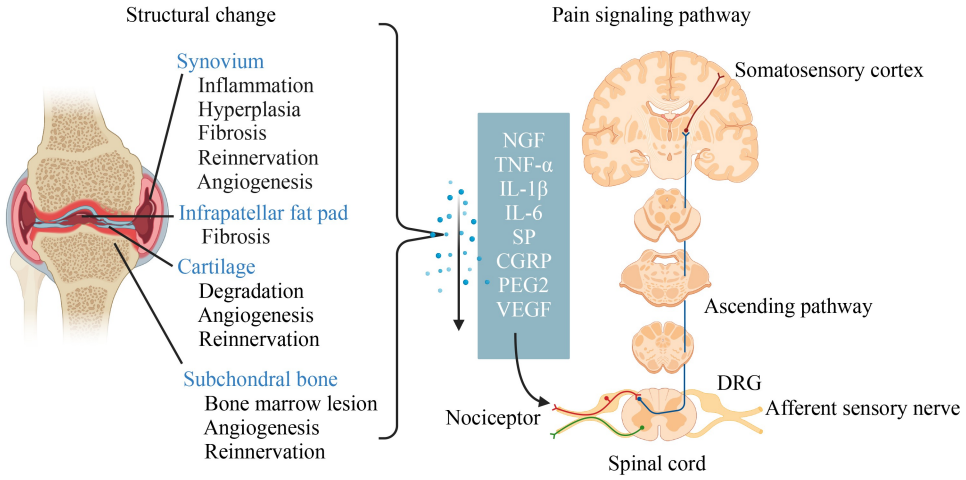

Fig. 1 Structural change and pain signaling pathway (nociceptive pain). Noxious stimuli generated from joint structural alteration can activate the pain nociceptors of the joint in the primary sensory nerve endings, which generate electrical signals that travel to the posterior horn of the spinal cord and ascend to the somatosensory cortex, resulting in the awareness of pain. NGF, nerve growth factor; TNF-α, tumor necrosis factor-α; IL-β, interleukin 1β; IL-6, interleukin 6; SP, substance P; CGRP, calcitonin gene-related peptide; PEG2, prostaglandin E2; VEGF, vascular endothelial growth factor; DRG, dorsal root ganglion. The illustration was created with Biorender.com.

magnetic nanoparticles have significantly reduced knee pain sensitivity when exposed to an alternating magnetic field via magnetothermal modulation of TRPV1 [33]. However, intra-articular injection of TRPV1 antagonist has also shown pain relief in OA by impeding the signaling pathway, which differs from the capsaicin [34]. Although both TRPV1 agonists and antagonists have shown improved efficacy in preclinical and clinical trials for pain management, attention must be given to adverse reactions [35]. Additional clinical trials and basic research are needed to explore the involvement of TRPV1 and the underlying mechanisms in OA pain and disease progression.

In addition to NGF, BDNF was also associated with the perception of pain in the knee joint. BDNF and its binding with high-affinity tropomyosin receptor kinase B (TrkB) are crucial in neuronal survival and the mechanisms of spinal sensitization linked to chronic pain [36]. Human OA synovial fibroblasts and macrophages express BDNF, and a significant increase in BDNF and TrkB levels was observed in the OA synovium [37]. Targeting the BDNF/TrkB signaling system could also be a potential therapeutic approach for alleviating OA pain.

Neuropathic pain

Neuropathic pain was redefined as “pain arising directly from a lesion or disease affecting the somatosensory system” by the International Association for the Study of Pain (IASP) in 2008 [38]. OA patients who exhibit a neuropathic pain component may represent a distinct phenotype [39]. No single symptom definitively diagnoses neuropathic pain; however, specific symptom combinations and pain descriptors can aid in identification [9]. The updated grading system for neuropathic pain has been widely adopted in research and clinical practice [40]. It incorporates a stepwise approach, including patient history, clinical examination, and diagnostic tests, to progressively increase the certainty that the pain is neuropathic. The full versions of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and Douleur Neuropathique en 4 Questions (DN4) screening tools were also utilized to detect neuropathic pain in OA, incorporating pain descriptors such as tingling, shooting, and burning sensations, along with bedside findings [41]. Additionally, the painDETECT tool proved valuable for identifying neuropathic pain in OA [41]. Neuropathic pain is frequently observed in patients with knee and hip OA, with a higher occurrence in the knee [42]. According to most studies, the occurrence of neuropathic-like pain in individuals with knee OA varied from 20% to 40% [42,43]. Nerve damage or dysfunction can lead to neuropathic pain characterized by abnormal signaling and central neuroplasticity [44]. Heightened pain intensity and disability are correlated with neuropathic-like symptoms in individuals suffering from knee OA [43]. There may be a positive correlation between local inflammatory indicators of effusion/synovitis, neuropathic-like pain, and indications of heightened pain sensitivity [45]. It has been shown that inhibiting CGRP activity can prevent sensitization and mechanical allodynia induced by neuropathic pain, but further validation is required [46]. Antidepressants and anticonvulsants, commonly used for depression and seizure disorders, have proven efficacy in treating pain conditions that do not adequately respond to conventional therapy, specifically neuropathic pain [47]. Duloxetine, venlafaxine, and milnacipran demonstrate

analgesic properties and potential anti-inflammatory effects separate from their mood-regulating effects, indicating their potential as pain-relieving agents [47]. Studies should focus on advancing our understanding of the mechanisms involved and identifying novel targeted interventions to effectively manage neuropathic pain in individuals with OA.

Nociplastic pain

Nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage leading to peripheral nociceptor activation or any identifiable disease or lesion of the somatosensory system as the cause of pain" [48]. The term "nociplastic pain" is used to describe chronic pain in patients who exhibit clinical and psychophysical findings indicative of altered nociceptive function. While central sensitization is considered the predominant mechanism underlying nociplastic pain, the potential contribution of peripheral sensitization cannot be ruled out [18]. Furthermore, nociplastic pain may coexist with neuropathic pain and, more commonly, with nociceptive pain mechanisms [49]. The presence of ongoing nociceptive pain appears to be a risk factor for the development of nociplastic pain, as hypersensitivity has been linked to prolonged nociceptive pain duration.

The IASP Terminology Task Force established four criteria for classifying and grading nociplastic pain within the musculoskeletal system [18]. A patient meeting all four criteria may be diagnosed with possible nociplastic pain [49]. In addition to the clinical features outlined, various questionnaires are available to assess nociplastic pain characteristics. Altered nociceptive processing in nociplastic pain conditions has been identified using semi-objective methods, such as quantitative sensory testing (QST), and objective approaches, including sensory evoked potentials and neuroimaging [49]. These objective assessments have revealed disruptions in cerebral pain-related activation and abnormalities in functional connectivity. QST may aid in assessing temporal summation and conditioned pain modulation, while offset analgesia and functional neuroimaging provide insights into alterations in cerebral pain processing [18]. The Central Sensitization Inventory (CSI) was designed to assess the presence of central sensitization in individuals with musculoskeletal pain [50]. However, it remains unclear whether the CSI reflects heightened nociceptive responses or a form of psychological hypervigilance [51]. Furthermore, abnormal scores on neuropathic pain questionnaires, such as PainDETECT, can assist in differentiating neuropathic pain features from those of nociplastic pain [42].

Non-pharmacological approaches, including patient education, lifestyle changes, psychological therapies, and treatment of comorbidities, should be the first line of intervention [52]. The pharmacological management of nociplastic pain shares similarities with that of neuropathic pain and typically involves the use of serotonin–noradrenaline reuptake inhibitors, gabapentinoids, and, traditionally, tricyclic antidepressants, but opioids and NSAIDs are generally ineffective [52]. A clinical study on a fixed combination of palmitoylethanolamide and melatonin demonstrated improvements in pain intensity, sleep quality, and overall quality of life, with no reported side effects in patients with nociplastic pain [53]. Potential future therapies include neuromodulation techniques and novel pharmacological treatments like cannabinoids.

Pain assessment and therapeutic approaches

Nociceptive pain in OA is typically characterized by localized, activity-dependent aching or throbbing [8]. Diagnosis is based on pain characteristics and physical examination findings, such as joint tenderness, swelling, and restricted range of motion. Imaging techniques, including X-ray to assess joint space narrowing and osteophytes, MRI to detect cartilage loss and bone marrow lesions, and ultrasound to identify synovitis and effusion, further support the diagnosis. Pain severity and functional impact are commonly evaluated using the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [54]. The McGill Pain Questionnaire (MPQ) provides qualitative descriptions of nociceptive pain, while the Knee Injury and Osteoarthritis Outcome Score (KOOS) offers a comprehensive assessment of knee pain and its effect on daily activities and quality of life [8]. Among pharmacological treatments, NSAIDs, such as ibuprofen and celecoxib, are the most effective for managing nociceptive pain in OA [16].

Neuropathic pain in OA is often described as a burning, tingling, shooting, or electric shock-like sensation [17]. Diagnosing neuropathic pain in OA involves identifying nerve involvement through clinical evaluation and supportive tests. A thorough patient history, focusing on pain patterns such as spontaneous pain or abnormal sensations, is crucial in distinguishing neuropathic pain from nociceptive pain. Physical examination may reveal signs such as allodynia or hyperalgesia [17]. The Neuropathic Pain Scale (NPS) and DN4 questionnaire assess key features of neuropathic pain, including burning, shooting, tingling, and electric shock-like sensations [41]. They also evaluate numbness or hypoesthesia, allodynia, and hyperalgesia [42]. The MPQ can also be used to evaluate the sensory quality of the pain, with common descriptors including burning, stabbing, or shooting. QST revealed a reduced pressure pain threshold near the affected joint in patients with

neuropathic pain [9]. Tricyclic antidepressants (TCAs), gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, have moderate-to-high quality evidence and strong recommendations, making them first-line treatment options [55].

Nociplastic pain, recognized as the third mechanistic pain descriptor, is characterized by widespread pain, fatigue, disrupted sleep, cognitive and mood changes, and heightened sensory sensitivity [52]. It often coexists with nociceptive and/or neuropathic pain and is linked to central nervous system alterations, particularly in brain regions involved in pain processing [18]. Individuals with nociplastic pain typically experience pain disproportionate to any peripheral pathology [10]. The pain is typically constant and tends to be diffuse, affecting a wide area of the body [52]. Non-pain symptoms are often valuable in providing diagnostic insights. Common non-pain symptoms include persistent fatigue, unrefreshing sleep, low mood, difficulties with concentration and short-term memory, and heightened sensitivity to visual, auditory, and tactile stimuli [56]. Key assessment tools for nociplastic pain in OA include the PainDETECT questionnaire, which helps differentiate nociplastic pain from other types by evaluating sensory changes and pain patterns [42]. Additionally, the CSI can assess the extent of central sensitization, a hallmark of nociplastic pain [50]. Simple analgesics and non-steroidal anti-inflammatory drugs have limited effectiveness in treating nociplastic pain. In contrast, centrally acting medications, such as tricyclic antidepressants (e.g., amitriptyline and cyclobenzaprine), SNRIs (e.g., duloxetine and milnacipran), and gabapentinoids, are recommended for managing nociplastic pain [18]. Additionally, stress reduction techniques, cognitive-behavioral therapy, and physical therapy are also recommended as part of the treatment approach [18].

Alteration of the joint structure

The structural alterations in the joint lead to the production of pro-inflammatory cytokines and other pain-inducing chemicals [54]. These substances activate sensory nociceptors through interactions with receptors and ion channels, modulate intracellular signaling pathways, and enhance ion channel activity, ultimately resulting in the sensation of pain [57]. A gap persists in the knowledge of OA pain in the local joint structure, called "structure-symptom discordance," with no therapies proven to alter structural progression and poor symptomatic management [58]. The pain experienced in OA patients is highly variable, with some individuals reporting severe pain while others may experience minimal or no pain despite radiographic changes. Knee pain was more prevalent in OA patients with Kellgren/Lawrence (K/L) grade 4 compared to those with K/L grades 2 and 3, despite the common weak correlation between radiographic images and pain severity [59].

Articular cartilage

In normal physiology, cartilage lacks blood vessels and nerves, so it is considered not involved in pain initiation. Bacon *et al.* concluded that the loss of cartilage thickness is linked to a minor increase in knee pain, an association partly mediated by the worsening of synovitis [60]. The direct impact of cartilage loss on pain is minimal, and chondroprotective treatment may not be practical for reducing pain [60]. Nevertheless, as OA progresses, nerve in-growth in articular cartilage is discovered [8]. The atypical newborn nerves are nociceptors that perceive pain signals and mediate neuro-cartilage interaction [8,61]. Inhibiting the neuro-cartilage interplay may effectively alleviate OA pain [61]. It was found that the voltage-gated sodium channel Nav1.7 in chondrocytes significantly influences chondrocyte biology, cartilage degradation, and pain in OA by affecting the intracellular Ca^{2+} signaling and chondrocyte secretome [62]. Inhibiting Nav1.7 in chondrocytes and peripheral sensory neurons within the dorsal root ganglion (DRG) can prevent cartilage loss and alleviate pain perception [62]. However, the alteration in the structure of articular cartilage and the pain associated with OA still require further verification.

Synovial tissue

Numerous chemokines, cytokines, and neurotrophins are elevated in synovial tissue and are thought to be associated with OA pain (Table 2). Synovitis, or synovial membrane inflammation, is strongly linked to pain severity in patients with knee OA [63]. It is distinguished by synovial hyperplasia, heightened synovial fluid production, and infiltration of immune cells [64]. Synovial hyperplasticity and fibrosis are known to be major factors in the development of joint pain and stiffness [65]. These immune cells in synovial tissue release pro-inflammatory cytokines, such as TNF-α, IL-1β, interleukin-6 (IL-6), and C–C motif chemokine ligand 2 (CCL2) [66]. Excessive pro-inflammatory cytokines and other pain-inducing chemicals in the synovial fluid initiate pain perception and promote overstimulation of the primary sensory neurons that innervate the afflicted joint, leading to peripheral sensitization [67].

IL-1β produced by synoviocytes (fibroblast-like synoviocytes and macrophages) significantly enhances the synthesis of prostaglandin E2 (PGE2) in the synovium following injury to the articular cartilage [68]. PGE2 is the primary contributor to inflammatory pain in the OA joint, acting through various receptors expressed

Table 2 The molecules involved in OA pain

Type	Molecule	Role in osteoarthritis pain
Chemokine	CCL2	Attracts monocytes/macrophage, enhances inflammation [69]
Cytokine	IL-1β	Promotes cartilage degradation, increases nociceptor sensitivity [66]
	IL-6	Promotes inflammation, contributes to joint damage [54]
	TNF-α	Stimulates the production of inflammatory mediators, degrades cartilage [70]
Neurotrophins	NGF	Sensitizes nociceptors, increases pain perception [71]
	BDNF	Sensitizes pain pathways [20]
Growth factor	VEGF	Contributes to synovial inflammation and pain, associated with increased nerve growth [72]

CCL2, C–C motif chemokine ligand 2; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor.

differently in peripheral sensory nociceptors and the spinal cord [54]. It also induces the expression of inducible nitric oxide synthase (iNOS) and IL-6, thereby sustaining synovitis and enhancing hyperalgesia. IL-6 secreted by fibroblasts is independently linked to OA pain and radiographic progression [54]. The upregulation of matrix metalloproteinase-1(MMP1) induced by IL-1β is also associated with symptomatic OA [54].

TNF-α accelerated the firing rate of sensory fibers in DRG, enhanced neural signaling in the spinal cord, and critically contributed to increased pain associated with a lower mechanical response threshold [73]. TNF-α secreted by synovial membranes or activated chondrocytes has been demonstrated to upregulate IL-6 production and the development of neuropathic pain in DRG and spinal cord [74]. Meanwhile, TNF-α in the synovial fluid activates macrophages and stimulates osteoclast proliferation and differentiation, closely related to OA pain [46]. Macrophages have a significant role in various inflammation-related processes, including the recruitment of leukocytes/lymphocytes, the proliferation of fibroblasts, the production of proteases, and the promotion of angiogenesis. These activities lead to the influx of cytokines and immune cells at the site of damage [75]. Therapies targeting pro-inflammatory mediators, such as TNF-α or IL-1β, have been proven ineffective in reducing the symptoms of OA [8]. Future studies should focus on developing more targeted and personalized interventions that consider the individual differences in the inflammatory response and the complexity of OA pain.

NGF plays a vital role in regulating chronic pain, as increased levels of NGF in the synovium are associated with OA pain [21,76]. It is a pro-inflammatory cytokine mediating pain signal transduction, which can lead to nervous system sensitization by binding to its receptor, TrkA, expressed on sensory nerve fibers [46]. NGF is reportedly involved in neuropathic pain states, with expression increasing during synovial inflammation, particularly when synovial tissues are exposed to TNF-α [70,71]. The mechanism of OA pain caused by NGF partially contributed to increased sensory innervation in the synovium membrane [77]. The phase II and phase III clinical trials demonstrated that anti-NGF antibodies yielded substantial enhancements in pain relief and functional improvement for OA patients [78]. However, it is crucial to acknowledge that the anti-NGF antibodies are also linked to an increased probability of encountering adverse events, including abnormal sensations, reduced sensitivity, and rapid progressive OA (PROA) in either the knee or hip [78,79]. Identifying risk factors for RPOA could enhance the safety and appeal of using anti-NGF antibodies in clinical practice for large joint OA and other chronic pain syndromes resistant to conventional treatments [78]. Inhibition of the interaction between NGF and its receptor has been shown to impair bony remodeling in osteoarthritic joints, suggesting that repurposing approved therapies that target bone resorption or enhance bone formation could be a promising approach to preventing or reducing the occurrence of RPOA [80].

The elevated vascular endothelial growth factor (VEGF) expression in the synovial fluid of the OA joint has been directly associated with increased pain intensity and disease progression [72]. VEGF is a powerful proangiogenic factor and a crucial mediator of new blood vessel formation [81]. VEGF receptor 1 (VEGFR1) mediates joint pain, while VEGFR2 is connected to cartilage degeneration [82]. Inhibiting VEGFR1 and VEGFR2 concurrently is an effective therapeutic approach that can quickly alleviate joint pain and protect joint tissue against deterioration [72].

Subchondral bone

Bone marrow lesions (BMLs) are commonly detected pathological features in the subchondral bone with the development of OA [83]. However, the association between BMLs and joint pain is ambiguous [84]. Previous clinical studies have indicated that BMLs significantly impact the OA pain generation in the knee joint [85]. Recent studies concluded that there is no

substantial association between the volume of BMLs and pain [86,87]. The connection between OA discomfort and cyst-like lesions in the subchondral bone also remained uncertain. Kornaat *et al*. suggested that subchondral cysts were unrelated to OA pain [88]. However, a recent clinical study concluded that subchondral cyst-like lesions are an independent factor contributing to pain in OA patients; osteoclastogenesis and nerve growth within these lesions may explain the associated joint pain [87]. During aberrant subchondral bone remodeling, osteoblasts secrete PGE2, which induces pain and promotes OA progression [89]. Targeted deletion of cyclooxygenase 2 (COX2), the primary enzyme producing PGE2, in osteoblasts, or the PGE2 receptor EP4 in peripheral nerves, significantly alleviates OA symptoms by decreasing the levels of the voltage-gated sodium channel Nav1.8 [89]. OA pain involves the additional recruitment of nerves innervating the subchondral bone at a later stage, making these nerves important targets for developing mechanism-based therapies to treat late OA pain [90]. The analgesic benefits of inhibiting TrkA, which reduces NGF activity, may be attributed to decreased pathological innervation of the osteochondral interface [91]. More clinical studies and meta-analyses are required to validate the correlation between BMLs and knee OA pain [1].

Since the pain processing pathogenesis concerned with the joint structural alteration of OA remains unclear, a comprehensive understanding of the mechanisms involved in structural pathology contributing to pain in OA is urgently needed.

Infrapatellar fat pad

Infrapatellar fat pad (IFP) fibrosis may potentially cause tissue alterations, disrupting the typical distribution of stresses within the joint during movement, leading to a deterioration of the condition and increased pain [92]. Evidence demonstrated that suppressing fibrotic alterations in the IFP relieved pain and mitigated articular cartilage degradation [93]. The IFP-synovial unit exhibited a notably greater number of vessels in OA patients, and the endothelin 1 (ET-1) generated by the endothelial cells can induce primary hyperplasia by stimulating the peripheral terminals of nociceptors [92]. ET-1 can enhance endothelin hyperplasia induced by stimuli via binding to ET receptors on endothelial cells, thereby increasing their sensitivity to mechanical stimuli and releasing pronociceptive mediators [94]. Piezo2, an ion channel that converts mechanical inputs into electrical impulses in the sensory perception of touch, proprioception, and pain, was highly expressed in the IFP-compartments in OA [95]. It has been identified as a mechano-transducer contributing to hyperalgesia induced by non-harmful stimuli, which might contribute to the pain generation in IFP of OA joint [92].

Pain sensitization in OA

OA is characterized by mechanical sensitization and joint pain during movement. Clinical studies have shown that individuals with OA experience mechanical sensitization not just at the diseased joint but also at locations far away from the joint, indicating the existence of both peripheral and central mechanical sensitization [96]. Sensitization is characterized by heightened reactivity and reduced pain threshold, resulting from the temporal summation of repeated stimuli that accumulate post-synaptic action potentials in nociceptors, amplifying the response [97]. Repetitive stimulation from local inflammation or mechanical stress of nociceptive fibers induces antidromic transport and triggers the release of SP or CGRP at the nociceptor during chronic pain, which subsequently activates macrophages, lymphocytes, or mast cells and contributes to increased inflammation and pain sensitization [97]. Pain sensitization has been observed in 46% of knee OA patients with chronic pain before or after total knee replacement [98]. Peripheral sensitization is linked to weight-bearing and non-weight-bearing pain, whereas central sensitization is associated only with weight-bearing pain [99]. Continuous noxious inputs from the OA joint can alter the pain signaling pathway and sensitize pain. Typical features include low-threshold excitation, misinterpretation of innocuous stimuli, hyperresponsiveness, and extended receptive fields. The characterized clinical manifestations of nociplastic pain are inconsistent pain intensity and nature to the injury or pathology of the OA joint, strong association with maladaptive psychosocial factors, and diffuse areas of pain [100]. In this case, conventional painkillers such as NSAIDs are ineffective, and the mechanisms involved appear crucial for pain management.

Peripheral nervous system

Long-term exposure to proalgesic mediators, such as pro-inflammatory cytokines and neurotrophins, can cause peripheral sensitization (Fig. 2). Within the knee OA joint, the interaction between the distal ends of dorsal root ganglion neurons (also known as knee neurons) and fibroblast-like synoviocytes, along with the inflammatory mediators they generate, is thought to facilitate peripheral sensitization [101]. Neuroinflammation in the DRG influences peripheral sensitization, and immune cells are vital in modulating pain sensitivity in knee OA [102].

M1 macrophages contribute to a chronic inflammatory microenvironment by releasing NGF, leading to reinnervation and hyperplasia [103]. It has been suggested that the sensitization of joint nociceptors

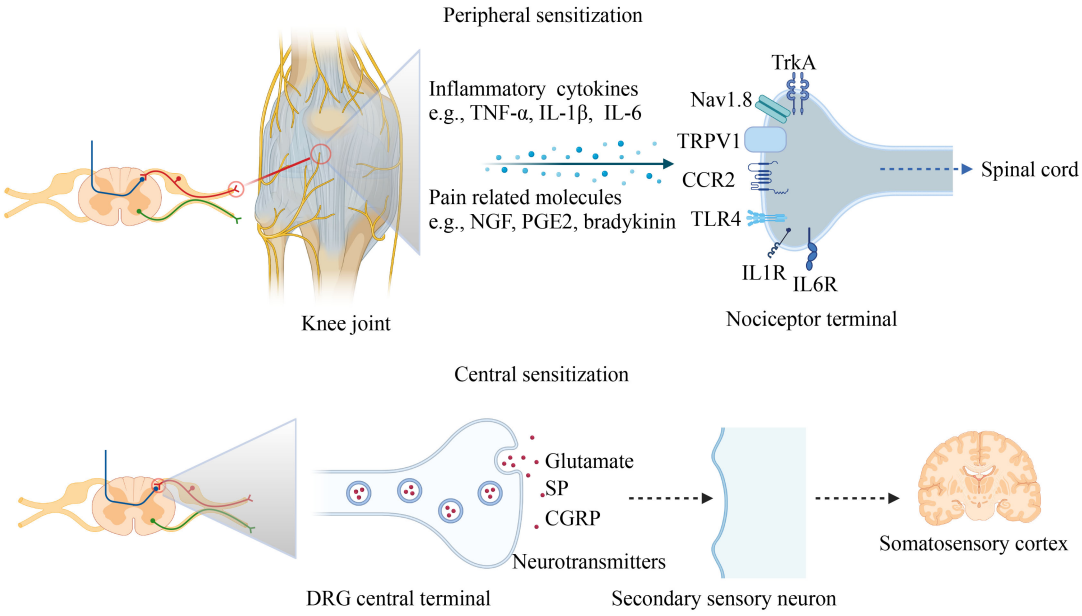

Fig. 2 Peripheral and central sensitization. Pain mediators and modulators, such as TNF-α, IL-6, IL-1β, and NGF, bind to their receptors, lowering the threshold for local nerve excitation and signal transmission, thus increasing the peripheral nociceptor's responsiveness. Glutamate, SP, and cytokines released from the central terminals of DRG neurons mediate neurotransmission to second-order postsynaptic neurons, relaying these signals to the brain. TrkA, tropomyosin receptor kinase A; TRPV1, transient receptor potential vanilloid 1; CCR2, C–C chemokine receptor 2; TLR4, Toll-like receptor 4; IL1R, interleukin1receptor; IL6R, interleukin 6 receptor. The illustration was created with Biorender.com.

mediated by NGF, crucial for osteoarthritic pain, also relies on Piezo2, making Piezo2 a potential therapeutic target for managing OA pain [104]. Suppressing the NGF/TrkA pathway can reduce pro-nociception and pain centralization [105].

Neuropeptides secreted from activated joint nociceptors may also cause peripheral sensitization [106]. It was discovered that increased DRG neurons in the A-δ and C fibers respond to subthreshold mechanical stimuli, implying that silent nociceptors may become sensitized to mechanical forces [107]. Silent nociceptors in the skin, muscles, viscera, and joints usually do not respond to minor stimuli. However, in pathological conditions, inflammatory cytokines and chemokines can decrease the activation threshold of these receptors, leading to the generation of pain sensations in response to stimuli that are typically below the threshold. Clinical trials targeting inflammatory factors, like IL-1β, IL-6, and TNF-α with monoclonal antibodies have not demonstrated significant analgesic effects [108].

CCL2 can contribute to hyperalgesia by interacting with its receptor C–C chemokine receptor 2 (CCR2), expressed by intra-articular sensory afferents, which is primarily responsible for attracting monocytes to sites of injury [69]. *Ccr2* knockout mice have not developed hyperalgesia, consistent with the pain relief effect of intra-articular CCR2 receptor antagonist injection [109]. Shingo *et al.* attribute this analgesic effect of the inhibition of CCR2 to significantly reduced macrophage infiltration in the innervating DRG [109]. M1-like macrophages accumulate in the DRG following joint damage, contributing to the persistence of OA pain independent of Nav1.8 nociceptors [110]. Inhibiting M1-like macrophages in the DRG can effectively alleviate chronic OA pain [110]. Neuroimmune interaction in the DRG is essential for pain generation and maintaining in OA [111].

Toll-like receptor 4 (TLR4) is a pattern recognition receptor that detects endogenous compounds called damage-associated molecular patterns, correlating to chronic pain in OA [112]. TLR4 antagonist therapy has shown efficacy in reducing movement-induced OA pain by decreasing the neurotoxic environment at the joint [113]. The damaged tissues of the OA joint interact with the innate immune system and the nervous system, accelerating disease progression and resulting in local structure remodeling. Constant neuroimmune interplay can shift the acute pain pattern to chronic pain independent of noxious stimuli, rendering classical analgesics ineffective.

A comprehensive understanding of the mechanisms driving peripheral sensitization holds promise as a target for OA pain management. In chronic OA, future research should focus on the neuroimmune alterations involved in the nociceptors and DRG.

Central nervous system

In knee OA, pain severity is often heightened by central

sensitization in the nociceptive transmission pathway, including facilitated pain ascending signaling and inefficient descending pain inhibition [114]. Central sensitization in OA pain is characterized by increased excitability and synaptic plasticity within the spinal cord and brain neurons, resulting in an intensified perception of pain and a decreased threshold for pain stimuli (Figs. 2 and 3). Apart from nociceptive pain and the involvement of peripheral mechanisms in chronic OA pain, central sensitization appears to be present in many OA patients [115]. The existence of central sensitization in OA patients is associated with deterioration of pain, worse functional impairment, increased anxiety, and depression [116]. Central sensitization persisted for 2 years after total knee replacement, leading to worse quality of life, greater functional disability, and higher dissatisfaction in these patients compared to those without central sensitization [117]. Chemokines and cytokines derived from injured tissues or immune cells are closely involved in developing and maintaining central sensitization [118]. Continuous and intense nociceptive inputs from the OA joint may result in complex changes in the central nervous system, which results in intensified nociception [119].

The distinguishing clinical features of central sensitization are hyperalgesia, enhanced temporal summation, and allodynia [120,121]. The central nervous system (CNS) can either enhance or suppress the transmission of pain signals by regulating the release of neurotransmitters and the activity of interneurons at the level of the dorsal horn [122]. Unlike acute and peripheral pain situations, which can be treated with NSAIDs and opioids, central pain disorders are most effectively managed with CNS neuromodulating drugs, such as SNRIs and anticonvulsants [123]. Moreover, the role of CNS components in pain perception may be affected by biological mechanisms such as infection or inflammation and psychosocial factors like emotional reactions and cognition [124]. Higher excitability of the nociceptive flexion reflex existed in severe OA patients, indicating central sensitization [125]. OA patients who reported larger areas of pain experienced more enduring and severe pain and higher levels of anxiety, suggesting altered central pain processing mechanisms [126].

SP, synthesized in the cell bodies of pain-sensing fibers of the DRG and subsequently transported and released into the spinal dorsal horn, acts via neurokinin 1 (NK1) receptors, playing a crucial role in conveying nociceptive sensations and enhancing pain sensitivity [127]. CGRP is believed to enhance glutamatergic signaling and induce a proinflammatory state in microglia within pain pathways, thereby contributing to the sensitization of sensory input and the experience of pain through CGRP receptor (CGRPR) found in myelinated A-fibers axon [128]. The N-methyl-D-aspartate receptor, a distinct subtype of ionotropic glutamate receptor, has been shown to have a role in neuronal excitation and the emergence of persistent pain sensations [129]. Nuclear factor-κB (NF-κB), a transcription factor for many proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, was found to be upregulated in the spinal cord, which is considered to be related to nociceptive pain and central sensitization in OA [118]. Meanwhile, in chronic OA pain, wide dynamic range (WDR) neurons located in the dorsal horn are activated by low-threshold mechanical stimuli and demonstrate hyperresponsiveness to high-intensity stimuli

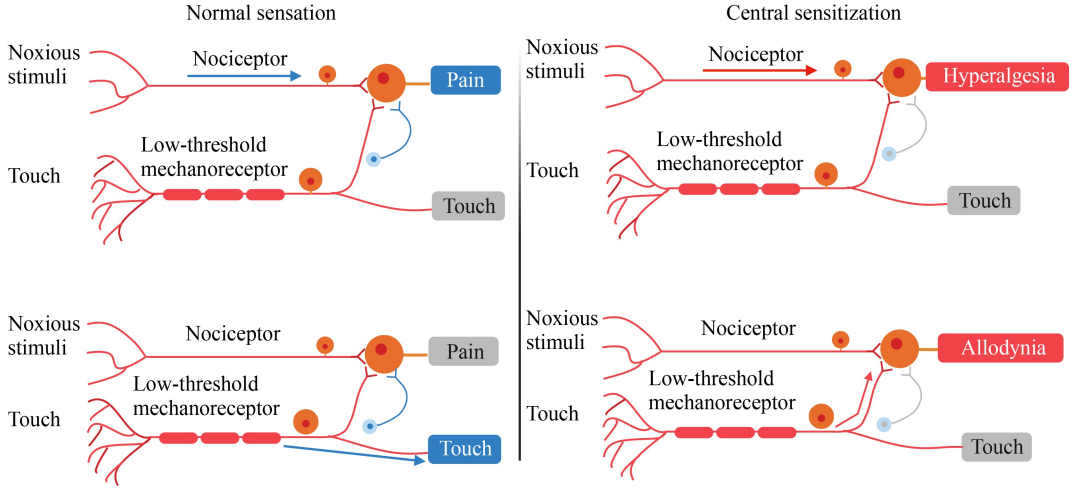

Fig. 3 Central sensitization. In normal conditions, tactile stimuli do not cause pain. In pathological conditions, central amplification heightens the intensity, duration, and spatial extent of pain responses to noxious stimuli. Additionally, it allows low-threshold sensory inputs to activate the pain circuit. In chronic pain, low-threshold mechanoreceptors can transmit innocuous stimuli to interneurons in the dorsal horn, which generate signals to the central nervous system, converting tactile touch into pain. The illustration was created with Biorender.com. Reproduced with permission obtained from Wolters Kluwer Health © Woolf, C. J. Pain (2011); 152, S2–S15.

[130]. The spontaneous and evoked firing of WDR neurons has significantly increased, and therapeutics inhibiting the firing of WDR neurons have provided pain relief in OA.

When exposed to injuries or inflammation, the microglial cells can be activated and induce neuroinflammation. Microglial activation in the spinal cord is a critical component of OA pain and can increase the expression of neurotrophic factors and inflammatory cytokines [131]. Growing evidence indicates that activated microglia in the spinal cord exhibit a substantial upregulation of cannabinoid receptor type 2, which is crucial in safeguarding the neighboring neural circuitry by modulating microglial activity and function [132]. The inhibition of microglial activation could be a potential target for pain management by suppressing the neuroimmune reaction [133].

The underlying factors contributing to chronic OA pain include the intricate interaction of peripheral and central systems, neuroplastic alterations, and the involvement of certain neurotransmitters and receptors. Understanding the clinical effects of central sensitization in OA patients and how it affects psychological comorbidities is essential for developing focused therapies.

Angiogenesis and reinnervation

Angiogenesis

Angiogenesis is critical in the pathogenesis of OA, allowing inflammatory cells to invade and increasing local pain receptors, contributing to structural damage and pain [134]. Unlike chondrocytes in healthy cartilage, which produce antiangiogenic factors, both hypertrophic chondrocytes and subchondral bone in the OA joint release NGF and proangiogenic factors, like VEGF, promoting angiogenesis and ensuing innervation [135]. A distinguishing feature of OA is enhanced angiogenesis in the subchondral bone, where blood vessels breach the tidemark and invade the avascular cartilage [64]. Abnormal angiogenesis driven by bone resorption promotes the spread of pro-catabolic and inflammatory mediators into the superficial articular cartilage, leading to cartilage damage during OA progression [136]. It was shown that heightened release of platelet-derived growth factor-BB (PDGF-BB) by mononuclear preosteoclasts leads to subchondral bone angiogenesis [137]. Blocking the PDGF receptor-β specifically in the subchondral bone, significantly reduces joint pain generation and OA development [138].

The synovium, meniscus, osteophytes, and osteochondral junction are common sites of angiogenesis and reinnervation [139,140]. Hypertrophic chondrocytes can result in cartilage neovascularization via the expression of signaling molecules like bone sialoprotein, which can stimulate endothelial cell migration, invasion, and adhesion [141]. Ramasamy *et al*. showed that endothelial cells had a proteolytic function that causes a misguiding in the direction of growth plate type H vessel extension in the proximal tibia [142]. It was indicated that the angiogenic activity in the subchondral bone occurs in the initial phase of OA, while the vascular invasion toward articular cartilage emerges later [143].

Proangiogenic factors, such as VEGF, are critical in the angiogenic process, which can induce the formation of new capillaries from pre-existing vessels, particularly under hypoxic conditions. Elevated VEGF levels are linked to increased OA severity and pain sensation [144]. Additionally, VEGF protein injections into knee joints cause OA-like joint pathology, while VEGF inhibition encourages cartilage regeneration by reducing angiogenesis in the joint [72]. Recent research suggests that the biological effects of VEGF signaling extend beyond its conventional role in promoting angiogenesis and vascular epithelial growth, indicating its potential involvement in pain transmission pathways [134]. Angiogenesis and inflammation are linked partially via VEGF [145]. Through direct effects on peripheral nerves, VEGF ligands induced nociceptive sensitization, and the activation of VEGF receptor-1 (VEGFR1) activation sensitized transducers of chemical stimuli, pressure and heat expressed in nociceptive terminals [146]. In OA patients, VEGF expression has increased in the synovial tissue and fluid, articular cartilage, and serum, which is critical in angiogenesis and correlated with pain, and anti-VEGF has received efficacy in OA pain relief [147]. It was demonstrated that intrathecal or intraarticular injection of an anti-VEGF monoclonal antibody targeting VEGFR1 reduced pain in advanced OA [148].

Subchondral bone remodeling and cartilage degeneration processes are related to angiogenesis and reinnervation, and inhibiting angiogenesis and nerve infiltration in OA joint may have anti-OA and pain-relieving effects [149]. The shared pathways of angiogenesis, reinnervation, and inflammation remain unknown, and the underlying mechanism needs to be investigated.

Reinnervation

During OA, nerve fibers frequently exhibit abnormal sprouting or increased neuropeptide expression [91]. Sympathetic and sensory nerves in the OA joint undergo dramatic distribution, density, and activity changes [135]. Vascular infiltration into articular cartilage is also linked to elevated NGF expression within the vascular channels, promoting subsequent sensory nerve invasion and pain sensitization [147]. NGF expression in the synovium increased in the early stages and declined in the advanced stages but continued to rise in the subchondral bone and osteochondral channels [21]. Axonal ingrowth that

expresses TrkA, driven by NGF, leads to irregular differentiation in osteochondral tissue [25].

It was indicated that the vascular invasion of non-calcified cartilage near the osteochondral junction correlates with the occurrence of sensory and sympathetic nerve innervation [150]. Sensory nerve fibers increasingly extend from the subchondral bone into the calcified cartilage zone or closely contact the articular cartilage [151]. Additionally, researchers have detected the presence of both sympathetic and sensory innervation within tibial osteophytes in OA [150]. It has been suggested that the elevated formation of osteoclasts and the growth of nerves within subchondral cyst-like lesions may contribute to the pain experienced in OA joints [87]. Reduced pathological innervation of the osteochondral interface may help explain the analgesic effects of TrkA-blocked NGF activity. Osteoclast activity can induce sensory nerve sprouting in subchondral bone and mediate the generation of OA pain, which is thought to be related to the molecules secreted by osteoclasts that can regulate axonal growth and even initiate pain perception, particularly the Netrin-1 signaling pathway [152,153]. Specifically, osteoclast-induced aberrant subchondral remodeling induces CGPR-positive sensory nerve outgrowth, and the upregulation of Nav1.8 located in the nociceptor terminals increases and synergistically generates OA pain with PGE2 synthesis stimulation [135]. In OA joints, blocking TrkA to suppress NGF activity prevents CGRP-positive sensory nerves from invading the osteochondral junction through bone marrow spaces, thereby reducing pain behavior [91].

In late-stage OA, synovitis potentially promotes pain sensation by fostering vascular and nerve invasion within deeper synovial layers, alongside the secretion of proalgesic substances such as NGF by synovial fibroblasts and macrophages [13]. Increased sensory innervation in the synovium was also observed [154]. The peripheral nerve fibers sprouting within the synovium are associated with heightened pain perception in OA [154]. It has been proposed that enhancing NGF/TrkA signaling within the peripheral sensory neurons and joint synovium promotes pain sensitivity and pain sensitization processing in the CNS [105].

Angiogenesis and reinnervation are crucial factors in the pathophysiology of OA pain. The aberrant sprouting and outgrowth of nerves within the joint contribute to enhanced pain signaling and sensitization mechanisms. Understanding the underlying mechanism may pave the way for novel therapeutic interventions to alleviate pain and improve patient outcomes.

Psychosocial and psychological factors

The discrepancy between the pathology of OA and the pain experienced, along with the variability in pain perception among individuals, indicates that a biopsychosocial network should be taken into consideration [155]. It was indicated that anxiety, catastrophizing, self-efficacy, depression, insomnia, and kinesiophobia are correlated with chronic OA pain [156,157].

The occurrence of comorbidity between pain and depression/anxiety in OA patients was demonstrated by Fonseca-Rodrigues *et al*. [158]. As anxiety and depression increase pain perception, a positive feedback loop is formed in which each disorder worsens the other two [158]. Depression has been linked to lower pain thresholds and tolerance for electrical, thermal, and pressure pain in the general population as well as in fibromyalgia and OA patients, and it has also been linked to patients' hyperalgesic responses [159]. Pain and depression are linked through potential biological pathways, but the specific mechanisms underlying their interaction are unknown [160]. The overactivity within the pathway linking the anterior cingulate cortex and subthalamic nucleus might have a major influence on the underlying mechanisms of comorbid chronic pain and depression [161]. The comorbid depression was associated with the current use of opioids in OA patients [162]. A meta-analysis and systematic review showed that selective serotonin-noradrenaline reuptake inhibitors, a class of antidepressants, can alleviate pain and disability in OA patients [163]. Duloxetine demonstrates efficacy in mitigating pain, boosting functionality, regulating mood, and improving overall quality of life when employed in OA treatment [164,165]. These findings imply that when contemplating the use of antidepressants, careful patient selection is necessary to maximize clinical advantages, considering the recognized likelihood of adverse events associated with antidepressant usage [166,167].

In individuals with hip OA, exacerbations of pain were linked to pain catastrophizing and beliefs in pain self-efficacy [168]. Pain catastrophizing hinders pain management and positive health practices, heightens focus on pain, intensifies pain processing in the central nervous system, and negatively affects society in a maladaptive manner [169]. Catastrophizing is believed to impact pain perception by increasing sensitivity and disrupting the descending inhibition pathway in the CNS [170]. Interventions that effectively address pain catastrophizing might reduce sedentary behavior and increase physical activity, offering long-term advantages for managing pain, improving physical function, and bolstering overall well-being [171]. Patients with greater pain self-efficacy beliefs, indicating their confidence in managing pain, exhibited reduced pain behaviors and reported lower pain levels [168]. Focusing on addressing pain catastrophizing and enhancing pain self-efficacy could prove advantageous in efforts to lower healthcare expenses for individuals suffering from knee OA [172].

For individuals experiencing OA alongside insomnia, integrating non-pharmacological sleep therapies into standard care is recommended [173]. Cognitive behavioral therapy, applied to older adults experiencing insomnia and OA pain, effectively enhanced sleep quality, reduced fatigue, and alleviated pain [174].

OA pain is influenced by a combination of psychosocial and psychological factors. These include cognitive and affective dimensions, social interactions, and engagement in life activities. Understanding and addressing these factors are crucial for effective pain management in individuals with OA.

Conclusions

OA pain is a complex, multifaceted process arising from tissue injury and modulated by the nervous system. It is typically classified as nociceptive, neuropathic, and nociplastic pain. Accurately identifying these pain mechanisms is crucial, as it enables targeted interventions that can improve patient outcomes.

Nociceptive pain, primarily driven by tissue damage and inflammation, responds well to NSAIDs, and structural changes should be emphasized in its assessment. In addition to painkillers, mechanism-based therapies, such as cartilage-protective treatments and antibodies targeting inflammatory mediators (e.g., IL-1β, TNF-α), should be prioritized. Conversely, neuropathic pain, resulting from nerve injury, and nociplastic pain, driven by peripheral and central sensitization, show limited response to NSAIDs. The Neuropathic Pain Diagnostic Questionnaire and LANSS scale can aid in grading neuropathic pain, while tricyclic antidepressants and gabapentinoids are effective treatments. Emerging strategies targeting NGF and CGRP hold promise in managing neuropathic pain. For nociplastic pain, SNRIs, low-dose antidepressants, and cognitive-behavioral therapy are commonly used to modulate central pain processing. CSI can assist in identifying central sensitization, while QST helps evaluate nociplastic pain. Additionally, functional and structural neuroimaging techniques (e.g., functional magnetic resonance imaging (fMRI) for assessing pain-related brain networks, and positron emission tomography scans for detecting neuroinflammation and glial activation) could enhance our understanding of nociplastic pain mechanisms.

Future perspectives

Until direct measurement techniques for pain mechanisms are further developed, expert consensus remains the best available approach to guide the identification of predominant pain mechanisms in both clinical and research settings. Importantly, many OA patients experience pain states where multiple mechanisms coexist, necessitating a multimodal assessment and treatment approach. Beyond OA, chronic pain is a hallmark of various musculoskeletal disorders, including rheumatoid arthritis (RA), chronic low back pain, and fibromyalgia, which exhibit overlapping mechanisms such as central sensitization, inflammation, and altered nociceptive processing. Recognizing these shared features allows for a broader application of pain assessment methodologies, including QST, clinical questionnaires, and imaging, in tailoring effective treatment strategies. Electrodiagnostic tools, like nerve conduction studies and QST, are commonly used to assess neuropathic pain by evaluating sensory pathway integrity. fMRI helps differentiate nociceptive pain from neuropathic pain by revealing distinct brain patterns. Additionally, biomarkers are gaining importance for diagnosis. For example, inflammatory markers like cytokines are being explored for predicting inflammatory pain in conditions such as RA.

To advance the understanding and treatment of OA pain, it is essential to identify emerging research directions that address gaps in current knowledge. Future studies should prioritize exploring novel mechanisms underlying OA pain, such as nociplastic pain and central sensitization, which remain underexplored in this context. Additionally, the development of personalized therapeutic strategies, considering genetic, environmental, and psychosocial factors, holds promise for more targeted and effective treatments. A focused exploration of potential therapeutic alternatives is crucial, given the limited long-term relief and significant side effects associated with current treatments. Regenerative medicine approaches, such as stem cell therapy and tissue engineering, could offer innovative solutions for repairing damaged cartilage and addressing the pathophysiology of OA. Furthermore, targeted drug delivery systems, including localized injections or nanoparticles, could enhance the efficacy of pharmacological treatments while reducing systemic side effects. Non-pharmacological interventions like neurostimulation, cognitive-behavioral therapies, and physical rehabilitation strategies also show potential for addressing both the physical and psychological dimensions of OA pain. For future studies to be methodologically rigorous and comparable, it is critical to define the key variables to measure, including pain intensity, joint function, inflammation levels, and disease biomarkers. The use of advanced measuring instruments, such as pain scales, imaging techniques like fMRI, and molecular biomarkers, will be essential for accurately assessing the efficacy of potential treatments. By focusing on these research priorities, future studies could yield novel, more effective, and individualized treatment options for OA pain, ultimately enhancing patient outcomes.

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Compliance with ethics guidelines

Conflicts of interest Lin Li, Xiwei Fan, Ross Crawford, Xinzhan Mao, Louis Jun Ye Ong, Feng Gao, Antonia Rujia Sun, and Indira Prasadam declare no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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