Mechanisms and Mediators of Pain in Chronic Inflammatory Arthritis

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Abstract

Purpose of the review Pain in chronic inflammatory joint diseases is a common symptom reported by patients. Pain becomes of absolute clinical relevance especially when it becomes chronic, i.e., when it persists beyond normal healing times. As an operational definition, pain is defined chronic when it lasts for more than 3 months. This article aims to provide a review of the main mechanisms underlying pain in patients with chronic inflammatory joint diseases, discussing in particular their overlap.

Recent findings While it may be intuitive how synovial inflammation or enthesitis are responsible for nociceptive pain, in clinical practice, it is common to find patients who continue to complain of symptoms despite optimal control of inflammation. In this kind of patients at the genesis of pain, there may be neuropathic or nociplastic mechanisms.

Summary In the context of chronic inflammatory joint diseases, multiple mechanisms generally coexist behind chronic pain. It is the rheumatologist's task to identify the mechanisms of pain that go beyond the nociceptive mechanisms, to adopt appropriate therapeutic strategies, including avoiding overtreatment of patients with immunosuppressive drugs. In this sense, future research will have to be oriented to search for biomarkers of non-inflammatory pain in patients with chronic inflammatory joint diseases.

Introduction

In rheumatology, in the context of inflammatory joint diseases, pain becomes an important clinical problem when it becomes chronic. Pain is defined chronic when it persists beyond normal healing times, and in these aspects of pathological duration, it lacks its physiological alarm functions connected to nociception. In temporal terms, the interval that defines the presence of chronic pain is the duration of more than 3 months. The definition of chronic pain in temporal terms is mainly intended to be clear for its proper operational application [1].

The importance of chronic pain in public health is extremely relevant, since it affects about 20% of the world's population, and up to one in five visits concerns chronic pain problems.

The classification of chronic pain is not simple and unambiguous. Over the past few years, major efforts have been made by the International Association of the Study of Pain (IASP) to try to classify chronic pain. The method followed by the IASP to categorize chronic pain in the context of the International Classification of Diseases (ICD)-11 framework establishes a hierarchical order starting from etiology, continuing with pathophysiological mechanisms and then the anatomical site [2•].

In chronic inflammatory joint diseases, pain is the pivotal symptom that leads the patient to the observation of the rheumatologist; its genesis and persistence often concomit multiple mechanisms independent of joint inflammation [3].

Although inflammatory joint diseases can be considered an emblem of nociceptive pain, therapeutic interventions in this regard are not always resolutive. Patients suffering from chronic inflammatory joint diseases may complain complex symptoms, frequently with neuropathic features (e.g., irradiated pain, burning sensations, tingling sensations) and often with evidence of signs of "centralization" characteristic of fibromyalgia [4]. A correct treatment of chronic pain, in inflammatory joint diseases, is essential to undertake the correct therapeutic strategy, mainly to avoid excessive and potentially harmful treatment with immunosuppressive drugs.

This review tries to summarize the main mechanisms and mediators that support pain in chronic inflammatory joint diseases, starting mainly from a pathophysiological point of view and the mechanistic categories currently proposed by the IASP (Table 1).

Nociceptive pain

Pain is defined by the IASP as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (<https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=10475>). This definition, updated in July 2020 after 2 years of work, is accompanied by six notes in which the definition of pain is further expanded. It is specified in one of these notes that pain and nociception are two distinct phenomena, and the experience of pain can occur independently of the activation of nociceptors. We will see later how this note is of particular relevance in chronic inflammatory joint diseases.

Nociception is the encoding and processing of noxious stimuli in the nervous system and, differently from pain, can be measured objectively (e.g., with electrophysiology). According to the IASP, pain is defined "nociceptive" when it arises from actual or threatened damage to non-neural tissue and is due to the activation of peripheral nociceptors.

Peripheral nociceptors are high-threshold neurons whose axons (thinly myelinated A δ or unmyelinated C fibers) innervate the skin, joints, and other deep tissues and visceral organs. Their cell bodies are located in the dorsal root ganglia. If activated by noxious stimuli, nociceptors activate ascending

Table 1. Current mechanistic pain terminology applicable in chronic inflammatory joint diseases

	Current definition	Year of formulation
Nociceptive pain	Pain that arises from actual or threatened damage of non-neural tissue and is due to activation of nociceptors	2011
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system	2011
Nociplastic pain	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain	2016

pathways through spinal cord, brain stem, and supraspinal structures in the thalamus and cortex. The conscious painful experience finds its roots in corticothalamic networks [5]. Moreover, from their sensory terminations, nociceptors can release the neuropeptide substance P and calcitonin gene-related peptide (CGRP), which induce a "neurogenic inflammation" [6].

Nociceptors can be stimulated by a plethora of noxious stimuli (mechanical, thermal, and chemical), including several mediators involved in the inflammatory process. These are the "classical" inflammatory mediators such as bradykinin and prostaglandins as well as pro-inflammatory cytokines, which have an increasingly recognized role in arthritis pain [7].

Rheumatoid arthritis

In rheumatoid arthritis (RA), pain typically arises from joint pathology and the consequent processing of nociceptive signals by peripheral, spinal, and supraspinal pathways. RA pain occurs either due to mechanical stimulation or spontaneously while the joint is at rest.

The inflammatory modifications of the articular environment which are the hallmark of the disease are characterized by the presence of several algogens (pain-producing agents) in the synovium and synovial fluid, which are capable of exciting or sensitizing peripheral nociceptors [8].

Prostaglandins

The hallmark of RA is synovitis, which classically causes pain with inflammation. It is well-known that synovitis is accompanied by increased prostaglandin production, which leads to the activation of thin unmyelinated C fibers of nociceptors in the synovial membrane.

Prostaglandin E2 (PGE2) has a predominant role in arthritis inflammatory pain. It derives from the hydrolysis of arachidonic acid by cyclooxygenases (COX-1 and COX-2). COX-2 can be induced in response to inflammation. PGE2 exerts its effects mainly through the activation of transient receptor potential vanilloid 1 (TRPV1), a ligand-gated ion channel that is expressed in nociceptors' cell membrane [9].

Cytokines

Several inflammatory cytokines can directly influence the responses of nociceptors [4].

Tumor necrosis factor (TNF) pronociceptive effect has traditionally been linked to stimulation of immune cells and consequent inflammation; however, there is evidence of a direct action on nociceptors [10^{*}]. TNF inhibitors have proven to reduce pain in mice model of inflammatory arthritis as soon as one day after their infusion, a time point when clinical and laboratory markers of inflammation were not yet affected by the drug [11].

Similarly to TNF, other cytokines such as interleukin (IL)-1, IL-6, and nerve growth factor (NGF) may play a key role in peripheral sensitization of nociceptors in rheumatoid arthritis [12–15].

Interestingly, on the other hand, some anti-inflammatory cytokines such as IL-10 may contribute to antinociceptive processes as well, reducing neuronal sensitivity [16, 17].

Anti-citrullinated protein antibodies

In a study by Wingerblad et al., mice injected with anti-citrullinated protein antibodies (ACPA) developed increased sensitivity to mechanical, heat, and cold stimulation, which lasted approximately 4 weeks, despite the lack of signs of inflammation. According to the authors' interpretation, these results might indicate that ACPA can directly induce pain via a mechanism distinct from inflammation [18^{••}]. Even if the nociceptive role of ACPA in RA patients is still to be fully understood, clinical evidences showing that some ACPA-positive subjects suffer from arthralgia in the absence of overt synovitis might represent an indirect confirmation of this hypothesis [19, 20].

Seronegative spondyloarthritis

Different from RA, nociceptive pain in seronegative spondyloarthritis (SpA) can characteristically be originated by the well-documented inflammatory involvement of periarticular and enthesal structures [21, 22].

Although IL-17 cytokine expression has been detected in several autoimmune and autoinflammatory diseases, it is considered one of the key element of SpA pathogenesis. Recently, resident populations of group 3 innate lymphoid cells and $\gamma\delta$ T cells have been identified at the human enthesis where they may produce the IL-17 that drives enthesitis [23].

It is noteworthy that IL-17, in addition to his role as a driver of enthesal inflammation, has proven to contribute directly to the enhancement of the sensitivity of nociceptors in animal models of arthritis [24].

Another cardinal domain of SpA is the axial component. In ankylosing spondylitis (AS), inflammatory back pain is one of the key clinical criteria for the classification of the disease [25]. Inflammatory back pain notoriously responds well to nonsteroidal anti-inflammatory drugs (NSAIDs), highlighting the central role of prostaglandins in its genesis and maintenance [26]. However, in non-responders, biologics are the indicated second-line treatment. TNF plays a key role in the axial disease, and there is solid evidence that TNF inhibitors are effective in reducing pain in SpA patients with axial involvement [27]. More recently, evidence indicating the involvement of IL-17 and IL-23 in AS has led to

the approval of treatments that target these cytokines in axial SpA [28, 29].

However, although pain in axial SpA has often been considered a surrogate marker for inflammation, it is not always related to inflammatory involvement or consequent damage, and evidence indicating direct sensitization of peripheral nociceptors from several immune mediators is growing [30, 31].

Crystal-induced arthritis

Joint pain in crystal-induced arthritis (gout and calcium pyrophosphate deposition disease (CPPD)) is mainly due to the inflammatory process triggered by crystal deposition in the synovial tissues. This inflammatory reaction tends to be intense, and it is often accompanied by unbearable pain.

Crystals do not directly stimulate nociceptors that are mainly activated via cytokines and other pro-inflammatory agents released in response to crystal deposition and the consequent leukocyte infiltration and activation [32].

The secretion of IL-1 β , as a product of Nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation, is the recognized fundamental pathogenetic moment of gout and CPPD acute arthritis [33].

The main pain-producing agents in crystal-induced arthritis are the prostanoids. Pathogenic crystals can rapidly induce COX-2, leading to the synthesis of PGE2 [34].

Other relevant contributors to the genesis of pain in crystal-induced arthritis are IL-1 β , bradykinin, and substance P (mainly released by sensory nerve fibers after TRPV1 receptor activation), which can cause peripheral and central sensitization [35–38].

Table 2 summarizes the main mediators of nociceptive pain in chronic inflammatory joint diseases.

Neuropathic pain

While it may be intuitive that chronic inflammatory joint diseases can cause pain by activating the mechanisms of nociception, perhaps more hidden are the mechanisms underlying the onset and persistence of neuropathic pain in these conditions.

In recent years, neuropathic pain has undergone an important redefinition that, as we will see later, has left a classification gap that has been closed with the definition of nociplastic pain [39••]. The definition of neuropathic pain excluded the concept of “dysfunction” of the central and peripheral nervous system and specified that the site of the dysfunction must be at the somatosensory system level, thus defining neuropathic pain as “pain caused by a lesion or disease of the somatosensory system” [40]. In chronic inflammatory joint diseases, different conditions affecting the somatosensory system can be detected.

First of all, joint inflammation can determine the presence of compressive neuropathies in various districts. Carpal tunnel syndrome (CTS) is an emblematic district pathology in RA. An ultrasound study conducted by our research group has shown that there are indicative signs of CTS in 26.3% of patients with RA. The main characteristic that differentiates an RA CTS from the idiopathic condition is the detection of an inflammatory pattern of synovial structures at the carpal canal level, linked to the presence of tenosynovitis of the flexor tendons of the fingers and/or the presence of synovitis of the radiocarpal joint.

Table 2. Main mediators of nociceptive pain in inflammatory arthritis

	PGE2	Bradykinin	Substance P	TNF α	IL-1 β	IL-6	IL-17	ACPA	NGF
Rheumatoid arthritis	+++	+	+	+++	+++	+++	+	++	+
Spondyloarthritis	+++	+	+	+++	-	-	+++	-	+
Crystal-induced arthritis	+++	+++	+	-	+++	-	-	-	-

Abbreviations: PGE2, prostaglandin E2; TNF, tumor necrosis factor; ACPA, anti-citrullinated protein antibodies; IL, interleukin; NGF, nerve growth factor

The transverse area of the median nerve in RA CTS tends to be smaller compared to the idiopathic condition [41]. An MRI study, performed on a small number of patients with PsA, revealed the presence of a pathological median nerve enhancement with soft tissue involvement in the carpal tunnel in as many as 80% of patients [42].

More rare, and prerogative of inflammatory joint diseases with significant anatomical damage to the elbow, is the cubital canal syndrome that can result in a compression of the ulnar nerve [43].

At the lower limb level, the most frequent compression neuropathy found in patients with RA is tarsal tunnel syndrome; also, this condition is more easily found in patients with long-term disease [44].

The damage that can be caused to the somatosensory system during RA also concerns axial structures. It is known that the most aggressive forms of RA can involve the craniocervical junction, with synovitic and erosive involvement of the upper cervical structures such as the atlanto-odontoid joint. Fortunately, a minority of patients develop compressive myelopathy secondary to joint damage to these structures [45]. However, the hypothesis of high cervical inflammatory involvement should also be well-taken into account in patients with early RA, since inflammatory signs of craniocervical junction inflammation are detectable on MRI in 24% of patients with a disease lasting less than 12 months. High disease activity, erosive disease, and ACPA are the predictors of early involvement of the craniocervical junction [46].

The mechanisms responsible for neuropathic pain in chronic inflammatory joint diseases, however, do not end with the presence of compressive neuropathies or compression on the axial structures. A recent literature strand has dealt with the presence of neuropathic-like features in chronic inflammatory joint diseases. Much used, for the detection of such symptoms, has been the Pain Detect Questionnaire (PDQ). PDQ is part of the symptom-based assessment tools for the evaluation of neuropathic pain, originally developed to discriminate between the neuropathic and nociceptive components in patients with chronic lumbar pain [47].

The use of this kind of instruments is becoming increasingly useful in characterizing pain in patients with chronic inflammatory joint disease. Data from the DANBIO registry, using PDQ, show that more than 20% of patients with chronic inflammatory joint disease complain of neuropathic pain features, 28% of patients with PsA, 21% of patients with SpA, and 20% of patients with RA, respectively [48•]. Percentages of neuropathic pain features similar to those of DANBIO in PsA were also found in other case series, where 25.4% of patients had PDQ results within the range of neuropathic pain. The main predictor of high PDQ scores was the presence of concomitant fibromyalgia [49].

Pain of probable neuropathic origin is found already in 13% of patients with early RA through PDQ, and the presence of neuropathic pain features is a negative prognostic factor for the achievement of disease remission at 1 year [50]. In contrast to what has been hypothesized so far that early arthritis was dominated by more "synovial" aspects, as a result of inflammation, it would seem that neurosensitization mechanisms can intervene precociously in the natural history of RA [8, 51]. Screening tools for neuropathic pain features are therefore useful in identifying pain mechanisms whose genesis goes beyond the presence of synovial inflammation or enthesitis.

The pathophysiological substratum underlying neuropathic pain features in chronic inflammatory joint diseases is certainly a topic of great interest and not yet clarified. At the basis of neuropathic symptoms, spinal cord mechanisms involving glial cells could also be involved. At the level of these cells, there is a deep interaction between the nervous and immune systems, and the conditions for the onset of neuropathic pain are created [52]. Pro-inflammatory cytokines, produced in abundance during chronic inflammatory joint diseases, such as IL-1 β , IL-2, IL-6, and TNF alpha, can activate glial cells, particularly microglia and astrocytes. Activated glial cells in turn have the ability to produce free radicals, nitric oxide, chemokines, cytokines, and neurotrophic substances. These mediators are able to determine neuronal damage and in turn amplify the paracrine activation of the glial cells [53, 54].

The inflammatory milieu that is created at the spinal level, much studied in the animal model, seems to be responsible for an important share of neuropathic pain during chronic arthritis. In the human being *in vivo*, it is difficult to study this type of painful mechanisms. In light of the current definition, being lesions substantially not provable with instrumental tests, they do not fall strictly under the neuropathic pain domain.

Obesity, which is more prevalent in patients with inflammatory arthritis than in the general population, is an additional risk factor for neuropathic pain [55].

Another mechanism that could play a role in the onset of neuropathic pain probably resides at the peripheral level, at the level of digital nerves. In the presence of synovitis affecting the metacarpophalangeal joints in patients with RA, the transverse area of the palmar digital nerves near the synovial inflammation appears enlarged. At the basis of these morphological alterations of the palmar digital nerves, it is assumed that there are mechanisms of perineuritis (unpublished data, personal observations).

Nociplastic pain

As mentioned above, among the notes accompanying the new definition of pain proposed by the IASP, it is specified that pain and nociception are two distinct phenomena, and that pain may be present in the absence of evidence of nociceptor activation. This phenomenon is particularly documented in chronic inflammatory joint diseases, where a significant proportion of patients suffer from concomitant fibromyalgia despite an optimal control of inflammation. Typical symptoms of fibromyalgia, *i.e.*, chronic widespread pain, non-restorative sleep, fatigue, together with the other typical symptoms of “fibro fog,” are present in a significantly higher proportion of patients with RA (18–24%), with PsA (18%), and with axial SpA (14–16%) [56]. The percentages may vary depending on the proposed diagnostic/classification criteria. However, the criteria of the American College of Rheumatology explicitly state that fibromyalgia may exist regardless of whether or not other diagnoses are present, specifically a chronic inflammatory joint diseases [57].

The pain of a concomitant fibromyalgia in the context of a chronic inflammatory joint disease falls within the domain of nociplastic pain. The concept of nociplastic pain was introduced in 2016, and originated from the redefinition of neuropathic pain once the concept of dysfunction was eliminated [39, 58]. In

patients with fibromyalgia, as in other “dysfunctional” pain conditions, i.e., without evidence of peripheral nociceptor activation and somatosensory system damage, there is abundant evidence of alterations in the central pain processing. The adjective “nociplastic,” deriving from the fusion of the terms “nociceptive plasticity,” was coined to reflect an alteration of the nociceptive pathways. In conditions characterized by nociplastic pain, there is no structural alteration demonstrable with the techniques currently available.

In patients with fibromyalgia, multiple mechanisms of central sensitization have been described, mainly characterized by changes in the volume of the gray matter in certain brain regions, alterations in the descending modulation pathways of pain, and increased activation of the pain matrix [59]. Several morphological changes in the brain of RA patients have been described, including an increase in the gray matter in the basal ganglia, structures involved in pain processing [60], but also numerous functional alterations. High levels of inflammation are associated with connectivity patterns that predict pain, fatigue, and cognitive dysfunction. These connections involve the inferior parietal lobule (and its gray matter reduction), the medial prefrontal cortex, and other encephalic networks [61].

In patients with fibromyalgia, the pathophysiology is still to be clarified, and, however, there are not only central sensitization mechanisms as explanation for painful symptoms. A segment of the literature of recent years has documented how, in about half of patients, there is a small fiber neuropathy [62], documented as reduced intraepidermal nerve fiber density (IENFD) with techniques such as histological examination on skin biopsy or corneal confocal microscopy [63, 64], more

Fig. 1. Pain mechanisms in patients with chronic inflammatory joint diseases. Three pathophysiological mechanisms of pain frequently coexisting in patients with chronic inflammatory joint diseases. The red circle contains the nociceptive mechanisms, represented in the figure by the ultrasound image of an active synovitis of a metacarpophalangeal joint in a subject with rheumatoid arthritis. The neuropathic mechanisms are enclosed with yellow circle, in this case documented by the ultrasound image of a median nerve markedly enlarged at the inlet of the carpal canal, indicative of a carpal tunnel syndrome in a subject with rheumatoid arthritis. In the gray circle, the nociplastic mechanisms of pain centralization are exemplified in case of concomitant fibromyalgia, magnetic resonance image of a morphologically normal brain.

recently alternative diagnostic modalities such as ultrasound of the sural nerve have been sought [65, 66]. The presence of a reduced IENFD conceptually falls within the “neuropathic” domain, leading to doubt that the definition of nociplastic pain is applicable to all patients with fibromyalgia.

It is essential to correctly diagnose fibromyalgia in patients with chronic inflammatory joint diseases: disease activity, more and more frequently measured by patient-reported outcomes, may be overestimated [67], especially in SpA where it may be difficult to distinguish between active enthesitis and tender points [68].

Conclusions

In this review, we have tried to show how pain, and in particular chronic pain, is a complex, amorphous, sometimes ambiguous, and often very difficult to interpret manifestation in the context of chronic inflammatory joint diseases. There is still no consensus as to whether to consider chronic pain a symptom or a disease itself. While a biomedical approach is necessary to establish the correct diagnosis of pain, the biopsychosocial implications (especially in terms of functional disability and distress) for its overall framework must be evaluated [69].

The concept that in chronic arthritis there is only one mechanism responsible for pain has now been overtaken by the concept of “mixed pain,” i.e., a condition in which in the same subject, several mechanisms are at the base of the symptom (Fig. 1). The definition of “mixed pain,” however, at the moment remains imprecise and does not exist from the taxonomic point of view [70].

The not easy task of the rheumatologist is to correctly frame the chronic pain, being able to bring relief to the patient and avoiding to prescribe potential treatments that are useless if not harmful.

Future research will have to be oriented to search for biomarkers of non-inflammatory pain in patients with chronic inflammatory joint diseases.

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Not applicable

Code availability

Not applicable

Author's contribution

MDC and GS drafted the article. All the authors revised it for the important intellectual content. All the authors approved the final version.

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Declaration

Conflict of Interest

Marco Di Carlo declares that he has no conflict of interest. Gianluca Smerilli declares that he has no conflict of interest. Fausto Salaffi declares that he has no conflict of interest.

Ethics Approval

Not applicable

Consent to Participate

Not applicable

Consent for Publication

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- Of importance
- Of major importance

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