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Targeting Pain or Osteoarthritis? Implications for Optimal Management of Osteoarthritis Pain

Joint pain, which may be a symptom of a wide variety of conditions, affects millions of people. Osteoarthritis (OA) represents the most frequent condition, affecting up to 20% of the population.[1] OA pain, like many other pain conditions, is associated with numerous misconceptions and erroneous beliefs about its causes and effective management. In fact, there are major difficulties in getting patients to describe their OA pain: they may think nobody wants to hear about it, or perhaps they feel the need to preserve their self-image and social image. Some people live their lives according to a self-imposed stoicism, and some perceive OA as a complex, ever-changing, illogical disease associated with aging.[2]

OA-related pain is a specific disease, with a complex pathophysiology, including neuropathic peripheral and central abnormalities, together with local inflammation involving all joint structures. Clinical findings emphasize that it is not a stable and linear condition,[2] that pain experience is independent of structural modifications, and that the quality of pain in OA is important to consider, aside from its intensity. OA-related pain is modulated by many factors, including the individual patient's psychological[3] and genetic[4] factors, as well as the theoretical role of meteorological influences. Recent neuroimaging findings have improved our knowledge about central mechanisms of OA pain, especially in persistent cases.[5] Potential targets for OA pain include OA-specific pathophysiological mechanisms, but there is more emphasis on pain pathophysiology. There is an urgent need to develop better analgesic drugs for people with OA pain, because the analgesics currently prescribed for OA target a variety of pain mechanisms, but they frequently fail to provide adequate pain relief, or patients may discontinue them because of adverse events. Experts expect that future treatments for OA pain will be developed more specifically according to OA pain pathophysiology. This review, based on literature research on pain and OA over the last 15 years, will summarize the most pertinent discussions and findings on this complex and disabling condition.

IASP's 2016 Global Year Against Pain in the Joints will address issues relevant to OA pain. IASP will disseminate recent validated findings on OA pain, not only to pain physicians but to all health care providers who treat OA pain.

Should We Treat Pain Or Osteoarthritis?

In 420 BC, Hippocrates described the *rheuma* (fluid) theory, whereby joint pain is driven by the brain. By sending more fluids to the lower parts of the body, the brain was thought to induce pain in all the lower limb joints.[6] This theory is now being revisited in the 21st century with recent findings of the importance of central mechanisms in OA pain, whereas previous investigations had focused mostly on peripheral mechanisms.[5,7]

Pain is an ubiquitous symptom in osteoarticular diseases, occurring much more commonly than stiffness or disability. OA of the knee, hand, or hip affects ~20–30% of adults in various populations[8] and is dramatically increasing in many countries, mostly related to age and obesity, leading to an increased number of people having OA

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pain, and creating a huge burden related to disability and health care costs.[9] Paradoxically, in comparison to the extensive research focus on inflammation and immunity in joint diseases, for many years joint pain pathophysiology received little attention, and numerous important research questions remain unanswered.[2] OA-related pain, classically considered to be a nociceptive pain condition, has been used as a major clinical model for the development of new analgesics dedicated to chronic pain. But clinicians have considered pain to be an alarm signal, correlated to the intensity of joint degradation. In OA, most authors have focused their studies on joint architecture and local degradation, considering pain as only a symptom, a consequence of joint damage.

What Do Animal Models Tell Us about Treating Osteoarthritis Pain in Humans?

In OA pain, as in any pain condition, research on animal models has tried to approximate the human condition. Preclinical testing is an important part of drug development, and animal models of OA[10] are commonly used for developing treatments for OA pain. However, animal models of OA have demonstrated weak specificity for predicting analgesic effects in humans, and several drugs that showed promise in preclinical studies have failed in clinical trials.

In fact, a more precise look at the literature demonstrates that most experimental studies on OA pain have been developed in inflammatory models, especially arthritis, comparing data in arthritic and control animals.[10] The term "osteoarthritis," which suggests inflammation, probably does not perfectly reflect the disease condition. In fact, in other languages, such as French and German, the terms "arthrose" or "arthrosis" seem more appropriate because their main connotation is not inflammation.

Several models of OA have been described, but these models were initially developed to analyze structural joint changes rather than to analyze nociceptive sensations in animals. Some models have also been developed to analyze nociceptive pain behavior, after cruciate ligament transection, meniscectomy, and monoiodoacetate injection.[10] However, the most frequent animal models of chronic joint pain are inflammatory models, such as Freund's adjuvant injection, carrageenan plantar injection, or urate joint injection. A review by Little and Zaki[11] includes a list of animal models that have been used to assess pain in OA animal studies. Interestingly, of the 112 studies targeting OA pain included in this review, 67% used injection methods or other methods that induced joint damage that "would not be widely accepted as typical of OA," while only 25% used surgically induced instability. This dichotomy between commonly published animal models of OA pain and those of OA histology limits the comparison of results between studies of interventions to target OA pain and structural progression of OA disease.

Experimental tests that can assess nociceptive behavior in animals are mostly represented by mechanical or thermal stimuli. Other tests are based on observations of spontaneous behavior, such as motility or writhing. As in all animal studies, translation to human beings is limited, and many animal findings have not been confirmed in humans.[12] Methods for pain assessment in animal models include measures of different types of OA pain, such as primary hyperalgesia (measured by joint tenderness on palpation or compression), allodynia (measured with temperature application or von Frey filament testing), and static or dynamic analysis of weight distribution between the arthritic and contralateral limbs.[12] In fact, there is an unmet need for validated, standardized methods for pain measurement in animal models of OA.

Where Does the Pain Come From? Joint Pain Receptors

The origin of joint pain remained unknown for a long period. In 1945, Davies reported the first experimental joint pain model and noted that the synovium was insensitive to pressure but that needle puncture induced diffuse intraarticular pain.[13] In 1950, Kellgren and Samuel studied pain induced by needles in the knees of healthy volunteers.[14] They demonstrated that the synovium was insensitive to needle punctures, but that the capsule and ligaments were sensitive to pain. Immunostaining has demonstrated the type of innervation of the joint.[15] The capsule, ligaments, meniscus, periosteum, and subchondral bone are largely innervated by a dense network of myelinated and unmyelinated fibers. The synovium is mostly innervated by unmyelinated fibers, although cartilage has no innervation; more than 80% of the fibers in the joint are unmyelinated fibers, equally distributed between C fibers and sympathetic fibers.

In the joint, there are four types of sensory organs.[15] Types I and II (corpuscular organs) are localized in the capsule, ligaments, and meniscus, but not in the synovium, acting as mechanoreceptors, sensitive to pressure and traction, and transmitting their message via myelinated fibers. Type III receptors, formed by thin A-delta myelinated fibers, are located on the surface of ligaments and act as high-threshold mechanoreceptors, responding to strong mechanical stimuli, and,

to a lesser degree, to thermal stimuli. Type IV receptors, also called polymodals, are formed by free terminals of unmyelinated C fibers and represent the most important type of joint receptors, found in all structures except cartilage. They are normally inactive and are called polymodals because they are activated by mechanical, thermal, and chemical stimuli in pathological conditions such as inflammation, as observed in OA. Type III and IV receptors are involved in pain sensation induced by joint lesions. They are also sensitized by increased intraarticular pressure and by local chemical changes.[15]

Pathophysiology of Pain and Osteoarthritis in the Joints

OA pain is classically considered as a nociceptive pain condition. Most studies on the nociceptive system are related to cutaneous nociception. By comparison, the nociceptive system of the joint has been less extensively addressed.[12] One important component of OA pain is mechanical pain. In a normal joint, intraarticular pressure is between 2 and 10 mm Hg.[16] In the presence of inflammation or local articular lesion, the pressure can rise to 20 mm Hg. Cartilage damage may induce hyperpressure of the subchondral bone,[17] and the joints contain specific nociceptors that are specifically activated by mechanical stimuli.

In OA, local inflammation is an important part of pathophysiology of the generation and maintenance of joint pain, involving the release of phospholipases, cyclooxygenases, lipoxygenases, leukotrienes, free radicals, and NO.[15] In the joints, C fibers express the TRKA receptor for nerve growth factor (NGF), the $P2X_3$ receptor for ATP, and also the glial-derived neurotrophic factor (GDNF) receptor. Mediators of these fibers are substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY), and vasoactive intestinal peptide (VIP) in all joint structures except the cartilage. NGF is an important component of C fibers, with an important role in joint pain, that is currently the target of new biological therapies.[18] The new class of anti-NGF agents have already demonstrated important analgesic effects in OA pain, that might, if adverse events are controlled, dramatically change analgesic strategies for OA pain.[18] Recently, receptors that play a role in neuropathic pain have also been found in the joints: TRPV receptors are present in many joint structures and can be the target of descending inhibitory mechanisms.[19]

Aside from nociceptors, other receptors in the joints may contribute to the mechanisms of joint pain and can represent putative targets for analgesics. For example, opioid receptors are present in the joints,[20] as are cannabinoid receptors,[21] and these receptors increase with inflammation.

Cannabinoid receptors may represent an important link between pain and OA pathophysiology. In a recent study,[21] systemic administration of a CB_2-receptor agonist attenuated OA-induced pain behavior and modified the changes in circulating pro- and anti-inflammatory cytokines exhibited in a model of OA. Analysis of the human spinal cord revealed a negative correlation between spinal cord CB_2-receptor mRNA and macroscopic knee chondropathy. These data provide clinically relevant evidence that joint damage and spinal CB_2-receptor expression are correlated. Activation of CB_2 receptors inhibits central sensitization and reduces its contribution to the manifestation of chronic OA pain. These findings suggest that targeting CB_2 receptors may have therapeutic potential for treating OA pain.

Central Mechanisms of Osteoarthritis Pain

Pain has a complex pathophysiology, and in OA, recent findings have demonstrated the important role of central mechanisms. In OA, as in all pain conditions, there is increasing evidence that central mechanisms and sensitization play an important role. In fact, central mechanisms could be involved mainly during late and chronic stages.[22] Interactions between the central and peripheral systems suggest a general plasticity of the nociceptive system in OA pain.[7] This plasticity may depend on different elements, such as emotional factors.

Brain Activation and Sensitization in Osteoarthritis Pain

Injection of a saline solution into the anterior tibialis muscle causes patients with knee OA to experience more intense and more diffuse pain compared to normal controls,[23] suggesting brain sensitization, as in many chronic pain conditions. Clinically, central sensitization related to joint pain induces pain in response to stimuli that normally do not induce pain (allodynia), with a larger area of pain activation and longer duration of pain.[22] Central sensitization in OA has been confirmed by quantitative sensory testing (QST) analyses and functional MRI.[5] Other findings have demonstrated that different types of OA pain could be related to activation in different brain regions. Spontaneous and continuous pain could be related to medial prefrontal-limbic cortical areas, regions that are involved in emotional state. Conversely, stimulus-evoked pain could be more related to somatosensory nociceptive processing regions. Brain sensitization observed in chronic OA may explain the postsurgical pain frequently observed after joint replacement, often concomitant with depressive symptoms.[24]

More recent studies have analyzed brain volume, specifically in certain areas, and found some modifications in gray matter. As in other chronic pain states, OA is associated with decreased gray matter,[25] but this decrease may not be permanent, since gray matter is regenerated 6–9 months after effective hip or knee surgery.[26]

Osteoarthritis Pain: A Relevant Biomarker for Joint Structural Damage?

One constant question in OA, both for patients and physicians, is the correlation between pain and joint damage. Many patients and their physicians believe that pain is correlated to joint damage and that intense pain may reflect a high degree of joint degeneration.

X-Ray Findings and Osteoarthritis Pain: More Than Just Joint Destruction

Cohort studies have demonstrated a modest correlation between pain intensity in OA and the degree of joint degeneration. A systematic review of the literature[27] showed that 15–76% of patients with knee pain had radiographic OA, and 15–81% of those with radiographic knee OA had pain. In a study pooling two cohorts, the Multicenter Osteoarthritis Study (MOST) and the Framingham cohort, Neogi et al.[8] demonstrated that pain was more correlated to joint space narrowing than with the presence of osteophytes. They also found that only high degrees of joint deterioration were associated with greater pain levels. In a prospective study involving 600 patients, Conaghan et al.[28] demonstrated that pain intensity (>60/100 on a visual analogue scale) was a significant predictor for joint replacement in knee OA, independently of joint structural modifications as assessed by the Kellgren and Lawrence Score.

MRI and Ultrasound Studies: Some Specific Structural Changes Are Associated with Osteoarthritis Pain

More precise studies with MRI have analyzed all joint components to investigate which structural changes were most strongly associated with pain in OA. Bedson et al.[27] demonstrated that synovitis and bone marrow edema were the structural changes that were most correlated with pain, whereas osteophytes, bone cysts, meniscal changes, and ligament tears were not associated with OA pain.

Studying patients with equal radiographic grades of knee OA, Wu et al.[29] demonstrated that inflammation features seen on ultrasound were positively and linearly associated with knee pain in motion. These findings show that synovitis is an important predictive factor for pain and may explain why corticosteroid injections are effective for pain in knee OA but seem to be most effective for effusions.

There is strong and increasing evidence from studies in humans that bone has an important role in the pathogenesis of OA. In particular, bone marrow lesions (BMLs) are recognized as a key feature of knee OA. A trial conducted in patients with only BMLs demonstrated that zoledronic acid (a potent bone-acting bisphosphonate) could decrease both pain and BML size over 6 months.[30]

In response to the question about whether pain can be predicted by structural changes in the joint, one may answer that on an individual basis, it is still not relevant to correlate pain to joint damage.

Osteoarthritis Pain Is Not Stable: Temporal Characteristics

Very few papers have described pain dimensions in OA, with little consensus.[31]

Pain intensity in OA is commonly assessed by numerical and visual analogue scales.[31] The McGill Pain Questionnaire (MPQ) has two different subscales, sensory and emotional, that may be used to differentiate both components, and has been validated in patients with hip and knee OA.

Woolhead et al. analyzed nighttime pain in knee OA[32] and also documented patients' views about knee OA pain. OA pain mainly occurs during the day and during physical activities, but a subset of patients may exhibit resting pain at night.

OA pain is not stable from one day to another, and it can be difficult to assess over a long period of time. In a study in 159 patients with OA,[33] we carried out correlation analyses for ecological real-time and recalled measures of OA pain and found that overall, recalled daily pain was strongly correlated with calculated 3-day mean pain assessment. Correlations between ecological and recalled measures were stronger for recall over the past 7 days than for recall over the past 28 days. The most reliable period for pain recall was 7 days, but the results obtained were influenced by current pain.

Longitudinal investigations that analyzed pain trajectories in OA found that knee pain changes little, on average, over 6 years in most subjects. Collins et al.[34] used data from 1753 participants with symptomatic knee OA. Group-based trajectory modeling identified five distinct pain trajectories, according to pain intensity, and showed that higher Kellgren and Lawrence grade, obesity, depression, medical comorbidities, female sex, non-white race, lower education, and younger age were associated with trajectories characterized by greater pain.

Osteoarthritis-Specific Pain Assessment Tools

A recent initiative from Osteoarthritis Research Society International (OARSI) and Outcome Measures in Rheumatology (OMERACT) has investigated several dimensions in OA pain, leading the development of ICOAP (Intermittent and Constant OsteoArthritis Pain), a new questionnaire including pain intensity, frequency, and impact on mood, sleep, and quality of life.[35] This qualitative approach explored changes in pain characteristics over time, in relation to the priorities and concerns of individuals living with hip or knee pain. The authors of this study defined two distinct pain conditions in OA, related to the context of OA progression, with intermittent and intense pain having the greatest impact on quality of life.

Although the authors proposed several pain descriptors, they did not intend them to be specifically used to define pain phenotypes in OA, as has been done in neuropathic pain. We have developed a qualitative analysis of OA pain with a new questionnaire, the OsteoArthritis Symptom Inventory Scale (OASIS), to characterize pain quality in OA, and in the future, to help to define different phenotypes of OA pain.[2]

Osteoarthritis Pain: Yet Another Neuropathic Pain Condition?

Recently, neuropathic characteristics have been investigated in painful OA, with different questionnaires such as PainDETECT and LANSS (Leeds Assessment of Neuropathic Symptoms and Signs).[36] Most studies have concluded that a neuropathic component is present in one-third of all patients with painful OA,[37] and some have also found that it could be associated with augmented central pain processing.[36] These neuropathic characteristics are associated with higher intensity scores and are a significant contributor to decreased quality of life. The question of whether OA pain is a neuropathic pain in some patients has emerged on the basis of these studies. In fact, neuropathic pain is classified as pain caused by a lesion or disease of the somatosensory nervous system. Neuropathy could contribute directly to OA knee pain through peripheral nerve damage within the joint, but there is currently no test by which to identify neuropathy within articular nociceptive pathways. Although several symptoms may suggest neuropathic mechanisms, it remains uncertain as to which questionnaire or which cutoff is most accurate in identifying neuropathic pain mechanisms in OA. In all cases, central processing observed in OA pain may augment pain severity and contribute to overlapping pain qualities associated with either nerve damage or joint damage.

Pain assessment has recently integrated more comprehensive measurements, such as quantitative sensory testing (QST). In OA, several studies have analyzed pain thresholds and pain sensitivity to different stimuli,[38] with most studies confirming central sensitization.[39]

Influence of Sex Differences, Movement, and Genetic Factors on Osteoarthritis Pain

In a cross-sectional analysis of 2712 individuals with OA pain (60% women), sex differences in pain severity at each Kellgren-Lawrence grade were assessed in both knees using a visual analogue scale and the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Women reported greater knee pain than men

regardless of Kellgren-Lawrence grade, although effect sizes were generally small.[40] These differences increased in the presence of patellofemoral OA and widespread pain. The strong contribution of widespread pain to sex differences in knee pain suggests that central sensitivity plays a role in these differences.

Hormonal changes may also be a factor that increases the severity of pain,[41] for example during menopause. Vitamin D deficiency has been considered as a putative factor for OA pain flares, but this possibility has not been confirmed in prospective studies.[42]

Another factor that has major implications on OA pain is exercise, along with joint movement. Movement may increase pain, but exercise is an important nonpharmacological approach to reducing OA pain. Exercise type and dose are essential considerations.[43] Pain at rest and pain on movement probably have a different pathophysiology. A recent study in patients developing chronic pain after hip or knee replacement demonstrated that chronic pain on movement after total joint replacement was strongly associated with the severity of pain on movement during the preoperative period.[44]

Pain is a subjective experience, and OA pain is under the influence of a variety of personal influences and coping strategies,[45] depending on the site of pain. As with all kinds of pain, OA pain is a condition in which mutual influences between pain and mood disturbances should be analyzed as part of patient management.[3] Additionally, weather conditions may influence OA pain sensitivity, with differences reported by age, gender, and country.[46] Lastly, genetic factors may modify pain experience and can also affect morphine consumption for analgesic purposes in knee OA.[47] Numerous genetic targets have been described—some for OA predisposition, and others for pain predisposition. One study has demonstrated interesting genetic mutations of TRPV1 receptors in the joints that may predispose individuals to OA pain and also to increased severity of OA disease.[19]

Obesity and Age: Epidemiology of Pain Or of Osteoarthritis?

Age and obesity are well-known factors for developing OA. In fact, obesity is also associated with OA pain intensity, and weight loss has been associated with a dramatic pain decrease in several prospective studies.[48] These findings may be explained by the association of weight loss with decreased mechanical loading of joints, yet pain also decreased in several non-weight-bearing joints, such as those in the hands.

Bliddal et al.[49] demonstrated that continuous reinforcement of a weight loss program can be successful in relieving pain for more than a year in obese patients with knee OA. In this study, weight loss was statistically associated only with a reduction in pain. Gudbergsen et al.[48] have demonstrated that the presence of joint damage did not preclude symptomatic relief following clinically relevant weight loss in older obese patients with knee OA. These findings suggest that pain relief induced by weight loss in OA may be related to modifications in pain pathways and not only to mechanical joint modifications.

Conclusion

Pain in OA involves complex mechanisms, intertwined with those of OA pathophysiology, yet also distinct. In the pathophysiology of OA pain, the joint is as important as pain-modulating systems and the brain. Only recently have pain physicians and rheumatologists shared their research to better understand this major symptom of OA. This collaboration has led to a better description of multiple mechanisms. As mentioned above, OA pain represents one of the most frequent pain conditions and is associated with disability, creating a huge burden to society. Translational research, from basic science to clinical research, from pain research to rheumatology, from patients to health care professionals, is important for the future optimal management of patients with pain and OA.

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