Osteoarthritis and Central Pain

Studies now confirm that osteoarthritis pain is affected not just by structural and inflammatory joint changes but also by central pain sensitization.

By Don L. Goldenberg, MD [1]

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Traditionally, osteoarthritis (OA) has been considered to be a peripheral pain disorder, related to progressive cartilage and bone damage, with little evidence for tissue inflammation. During the last decade, however, there has been greater appreciation of the inflammatory aspects of OA, including contributions from various cytokines and nociceptors, such as nerve growth factor. There is now a growing appreciation of the role of peripheral and central pain sensitization in OA, which will be the focus of this review.

OA and Pain Sensitivity

Pain sensitivity and intensity are magnified in OA. In fact, patients with OA, compared with normal controls, report increased pain intensity in widespread areas, including referred and radiating pain. In a study by Kosek et al, the researchers found an increased sensitivity to pressure, ischemia, and innocuous warm stimuli at the affected OA hip and at the contralateral hip in patients with OA. In addition, hyperalgesia has been reported in both the affected knee and the tibialis anterior muscle in patients with knee OA.

To see how pain affects the brain, 12 patients with knee OA underwent positron emission tomography
(PET) of the brain, using 18F-fluorodeoxyglucose. Scanning was performed during 3 different states: arthritic knee pain, experimental knee pain, and pain-free. Both pain conditions activated the pain matrix as seen on PET, but arthritic pain was associated with increased activity in the cingulate cortex, the thalamus, and the amygdala. These areas of the brain are involved in the processing of fear and other emotions, and in aversive conditioning. The study authors proposed that although arthritic pain and experimental pain activate similar areas of the brain, arthritic pain is also associated with areas of the brain implicated in affect, aversive conditioning, and motivation.

Researchers have found that there were significantly lower pressure pain thresholds (PPTs) over multiple joint, muscle, and soft tissue locations in patients with knee OA than in healthy controls. The lower PPTs correlated with higher pain intensity, higher disability, and poor quality of life scores.

For all locations (knee, leg, and arm), significantly negative correlations between pain sensitivity and PPT were found (more pain, more sensitization) in a study by Arendt-Nielsen et al. The OA patients studied showed a significant facilitation of temporal summation from the affected knee and had significantly less diffuse noxious inhibitory control as compared with controls. Moreover, the clinical/experimental pain parameters correlated poorly with standard radiological findings. A systematic evaluation of studies in painful OA found that compared with controls, OA subjects had lower PPTs both at the affected joint and at remote sites. Using quantitative sensory testing (QST), assessing PPTs had “good ability” to differentiate between patients with OA and healthy controls. In 168 adults with symptomatic knee OA, QST was used to measure sensitivity to heat pain, pressure pain, and cold pain, as well as to the temporal summation of heat pain, a marker of central sensitization. Pain hypervigilance was associated with greater clinical pain severity, as well as greater pressure pain. Pain hypervigilance was also a significant predictor of temporal summation of heat pain. Compared to controls and a low-symptom group, OA patients with increased pain severity were more sensitive to supra-threshold heat stimuli, blunt pressure, punctuate mechanical, and cold stimuli. Individuals in the low symptomatic OA group exhibited experimental pain responses similar to the pain-free group on most measures. Mechanical knee stimulation in patients with OA was associated with bilateral activity in the thalamus, as well as the secondary somatosensory, insular, and cingulate cortices, with unilateral activity in the putamen and amygdala. These data suggest that painful stimulation in subjects with OA of the knee engages many brain regions commonly observed in acute pain.

**Why Joint Images Don’t Always Match OA Pain**

In OA, the pain intensity often correlates poorly with the severity of peripheral joint damage. For example, 30% to 50% of individuals with moderate-to-severe radiographic changes of OA are asymptomatic, and 10% to 20% of individuals with moderate-to-severe knee pain have normal findings on radiography.

In one study that examined this paradox (Table 1), the investigators found significantly heightened pain sensitivity in high pain/low knee OA (Kellgren x-ray) grade subjects, while the low pain/high knee OA Kellgren grade group were less pain-sensitive. The results suggest that central sensitization in knee OA is especially apparent among patients who report high levels of clinical pain in the absence of moderate-to-severe radiographic evidence of pathologic changes of knee osteoarthritis.
In addition, PPT and temporal summation were associated with OA-related pain, but not with radiographic evidence of OA. A study of functional magnetic resonance imaging (fMRI) of the brain compared images taken while 11 participants with moderate/severe right OA pain performed motor tasks involving isolated isometric muscle contractions of quadriceps (knee), tibialis anterior (ankle), and finger/thumb flexor (hand) muscles and compared them with images from 7 asymptomatic controls. Differences in the organization of the motor cortex in knee OA were demonstrated in relation to performance of knee and ankle motor tasks and were related to quality of performance of the knee motor task. These results highlight the possible mechanistic link between cortical changes and modified motor behavior in people with knee OA.

In another study, structural MRI data were acquired from 26 patients with knee OA and 31 healthy individuals (controls). The data showed that the normalized volumes of bilateral caudate nucleus were significantly smaller in the group with knee OA than in the control group; and there was a trend toward smaller volume of the hippocampus in OA patients compared to controls. Detailed surface analyses further localized these differences with a greater involvement of the left hemisphere for the caudate nucleus.

Twenty-three subjects with knee osteoarthritis and 23 healthy controls underwent studies to measure pain thresholds to pressure, cold, and heat at the knee, ipsilateral heel, and ipsilateral elbow. Osteoarthritic subjects demonstrated significantly increased sensitivity to both pressure (Table 2) and cold stimuli, compared with controls. A similar pattern was noted at the pain-free ipsilateral ankle and elbow, indicating widespread pressure and cold hyperalgesia.
**Biomarkers and Pain**

Arendt-Nielsen et al found a correlation between central pain sensitization and biomarkers in OA. In the study, 281 patients with different degrees of knee pain intensity and radiographic findings were included. Serologic biomarkers, including high-sensitivity C-reactive protein (hsCRP), matrix metalloproteinase (MMP)-mediated breakdown of CRP (CRPM), MMP-mediated degradation of type I collagen (C1M), C2M, and C3M, were measured as well as PPTs, temporal summation of pain, and conditioning pain modulation (CPM).

The researchers observed correlations between the pain biomarkers, PPT, temporal summation, and CPM and maximal pain intensity measured during the last 24 hours. Significant associations between most of the serologic biomarkers were observed by the researchers. Interestingly, a high CRPM level was associated with centralized sensitization (temporal summation and CPM). However, none of the serologic markers correlated with the intensity or duration of knee pain, and only hsCRP correlated with the radiologic OA grade. Women constituted more of the most-sensitized group, and the least-sensitized group contained more men than women.

In a separate study, Arendt-Nielsen et al found that patients with high knee pain but low radiologic grade OA showed signs of pain sensitization. These patients showed significant associations between clinical knee pain intensity/duration and lowering of PPTs, facilitation of temporal summation, reduction of function, and high pain sensitivity index. The index classified 27% to 38% of the OA patients and 3% of the controls as highly sensitive with no association to radiographic OA. The index increased for high knee pain intensities and long pain duration.

**OA of the Hand**

Pain hypersensitivity has also been demonstrated in localized thumb OA. PPTs were significantly decreased over the first carpometacarpal (CMC) joint and the hamate bone but not over the lateral
epicondyle in patients with thumb CMC OA as compared with healthy controls. Patients with unilateral thumb CMC OA exhibited bilateral pressure pain hyperalgesia in both hands compared with healthy people. PPTs were not significantly associated with the intensity of pain.\(^{19}\)

In subjects with painful OA of the CMC joint, regional cortical blood flow (rCBF) increases were identified in the primary and secondary somatosensory, insular, and cingulate cortices; thalamus; amygdala; hippocampus; and dorsal midbrain/pontine tegmentum, including the periaqueductal gray/nucleus cuneiformis.\(^{20}\) The rCBF differences in the OA group in the postcentral, rostral/subgenual cingulate, mid/anterior insular, prefrontal, and premotor cortices were related to changes in perceived ongoing pain.

**Treatment**

Subjects with OA awaiting joint replacement displayed psychophysical features and functional imaging studies consistent with central sensitization.\(^{21}\) The OA patients had significantly lower threshold perception to punctate stimuli and were hyperalgesic to the noxious punctate stimulus in areas of referred pain. Functional brain imaging demonstrated significantly greater activation in the brain stem of OA patients in response to punctate stimulation of their referred pain areas compared with healthy controls, and the magnitude of this activation positively correlated with the extent of neuropathic-like elements to the patient’s pain, as indicated by the PainDETECT score.

There is evidence that central pain can be reversed after joint replacement.\(^{21,22}\) In one study, significant differences in brain gray matter volume between healthy controls and patients with painful hip arthritis were noted at baseline. Areas of the thalamus in patients with chronic OA pain exhibited decreased gray matter volume. When these preoperative changes were compared with the brain morphology of the patients 9 months after surgery, the areas of reduced thalamic gray matter volume were found to have “reversed” to levels seen in healthy controls.\(^{21}\) Another study found that after OA subjects underwent a knee replacement, there was a reduction in widespread hyperalgesia with normalization of PPTs (Table 3).\(^{22}\)
Indirect evidence for central pain mechanisms in rheumatic diseases can be found in therapeutic trials and preoperative patient characteristics. For example, duloxetine has been found to provide modest analgesic relief in knee OA.\textsuperscript{23} Duloxetine (60 to 120 mg daily), compared with placebo, resulted in a greater reduction in pain, improved function and patient-rated impression of improvement, and acceptable adverse effects for the treatment of knee OA pain after approximately 10 to 13 weeks of treatment.

In addition, Brummett et al recently published an article that showed that fibromyalgia characteristics, as determined by the 2011 fibromyalgia survey questionnaire, predicted poorer long-term pain relief after total knee and hip replacements—even among patients who did not meet specified criteria for fibromyalgia.\textsuperscript{24} The authors hypothesized that patients with an increased pain perception, as occurs in conditions such as fibromyalgia and OA, may account for decreased responsiveness to primary knee and hip arthroplasty. The study found that a higher fibromyalgia survey score was independently predictive of less improvement in pain. The fibromyalgia survey score was also independently predictive of change in overall pain and patient global impression of change.

**Conclusion**

There is strong evidence that osteoarthritis has components of both peripheral and central sensitization. Central pain sensitivity impacts disease activity and should be factored in management of this disease. In OA, measures of pain sensitivity improve with joint replacement.

**References:**


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