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Neuromuscular Function in Painful Knee Osteoarthritis

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Abstract Pain is a major cause of impaired mobility in elderly patients with chronic osteoarthritis (OA) of the knee. Central sensitization and impaired nociceptive inhibitory mechanisms have both been identified as contributing factors to heightened pain in this patient population. While central sensitization has been shown to produce enhanced pain responses and spread of pain to adjacent and remote body regions, conditioned pain modulation has also been shown to be adversely affected, and may be characteristic of those patients with chronic pain. Alterations of quantitative sensory testing measures have been demonstrated in patients with knee OA, and may serve as a clinical means of staging chronic musculoskeletal pain, including assessment of hyperalgesia and hypoesthesia. In addition, pain and altered somatosensation commonly associated with OA may be correlated with functional deficits.

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Introduction

Osteoarthritis (OA) of the knee has classically been defined as a progressive disorder of the articular cartilage. However, more recently it has been described as a disease of the knee joint "organ,' affecting cartilage, bone, ligament, synovium and periarticular musculature [1]. Progressive joint degeneration, observed via radiographic imaging, is a hallmark of OA and may be accompanied by intermittent but recurrent inflammatory flares. This synovial inflammation may be the driver behind patient symptoms such as pain and stiffness [2, 3••]. Knee OA has been associated with one or more of the following signs and symptoms: range of motion (ROM) loss [4], proprioceptive deficits [5], instability [6], periarticular muscle weakness [7], gait deviations [8], and pain. While nearly half of patients with radiological features of OA have no symptoms [9], it is the patient with painful OA that is most likely to seek medical attention.

Pain is the major symptom of OA leading to impaired function and decreased quality of life. In elderly individuals with knee OA, pain is the leading cause of impaired mobility [10]. While there is evidence that individuals with increased levels of radiographic changes often present with greater symptoms [11], several clinical studies have found that OA pain does not correlate to radiographic evidence of the disease. These latter findings suggest that pain and joint structural changes may be separate but related disease processes [12, 13]. Two important mechanisms have been

recognized as possible contributors to heightened subjective reports of pain in chronic knee OA. First, central sensitization of nociceptive pathways has been demonstrated in this population [14, 15], and has been shown to produce an enhanced pain response and spread of pain from the source of insult (primary hyperalgesia) to adjacent and remote body regions (secondary hyperalgesia); these findings suggest that knee OA may promote state of chronic, widespread pain in individuals with this disease. Secondly, studies have also demonstrated faulty and ineffective pain inhibitory mechanisms in persons with knee and hip OA [14, 16••]. Alteration of these central mechanisms may serve as the trigger for transition from acute to chronic pain.

Joint trauma is a known predisposing factor for the onset of OA [17], and it has been suggested that all OA is likely the result of some type of musculoskeletal insult, whether identifiable by the patient or not [13]. Knee joint injury in the young athlete has for many years been approached as a mechanical impairment, managed either through surgical repair or through replacement of damaged tissues (e.g., anterior cruciate ligament reconstruction), for the purpose of regaining the normal biomechanical properties of the joint. The recovery of mechanical joint stability has allowed the successful return to function, at least in the short term, for many patients following surgical repair/reconstruction. A second motive of the surgical repair/reconstruction of the knee has been to prevent/delay osteoarthritic joint degeneration [18], with some evidence supporting this notion [19]. However, in recent years some studies have begun to report the long-term outcomes of these surgeries, and have demonstrated that the onset of OA is not delayed, and may possibly be accelerated [20–22]. Considering the increasing incidence of knee OA [23] and the substantial functional deficits associated with knee OA [23], understanding the mechanisms underlying both the disease process related to impaired neuromuscular function and altered sensory processing underlying changes in functional performance is warranted.

Altered Nociceptive Function in Knee OA

Spinal Hyperexcitability

Central sensitization is described as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input leading to hyperalgesia [24]. This hyperexcitability occurs at the spinal and supraspinal levels and augments noxious input from the joint, thereby increasing the pain response [1]. Such hyperexcitability may present with different time courses, as wind-up (i.e., temporal summation) and short-term sensitization (homosynaptic or heterosynaptic) may occur at very different time courses. Withdrawal reflexes have been used comprehensively in pain research as an index of nociceptive responsiveness in both animal model and human studies (see [25, 26] for reviews). Importantly, the reflex is known to be 'modular,' meaning that the organization of the reflex is dependent on site of stimulation [25, 27] and phase of the gait cycle during ambulation [28]. The motor response to a noxious stimulus is to withdraw or pull away from the stimulus, which may involve activation of the flexor or extensor musculature, depending on the functional needs of the organism [29].

In humans, the reflex is typically elicited via electrocutaneous stimulation to the sural nerve or the medial arch of the foot [26]; however, some studies have used a very detailed stimulation montage as a means of characterizing the reflex response [30, 31]. Objective quantification of the reflex is determined through electromyographic (EMG) of involved musculature, such as the tibialis anterior or hamstring muscles.

Using the flexor withdrawal reflex (FWR) as a measure of spinal excitability, central sensitization has been reported in many chronic musculoskeletal conditions, including in patients with whiplash associated disorder [32, 33], fibromyalgia [32], and knee OA [15, 34], and in patients following anterior cruciate rupture [35]. While the FWR is commonly used in animal model studies [36, 37], one advantage of using this method in patient populations is the opportunity to monitor subjective pain responses with quantitative measures of nociceptive reflex excitability. In individuals with knee OA, it was found that a measure of spinal excitability (i.e., FWR threshold) was not correlated to resting levels of pain; even in patients without resting symptoms, heightened reflex excitability was demonstrated [15]. The drivers of this persistent heightened spinal excitability are not fully understood, although inflammation and aberrant joint loading are known peripheral components of this process [1].

With central sensitization, neurogenic inflammation can occur. Neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) are expressed, which can induce vasodilation and plasma extravasation at the site of musculoskeletal insult. Kidd et al. [38] demonstrated that plasma extravasation was enhanced bilaterally following induction of monoarthritis in an animal model. Of interest, these authors proposed that this mechanism might explain not only the contralateral spread of pain, but also the symmetrical spread of arthritis that patients sometimes experience.

With sustained nociceptive input, phenotypic changes in Aβ (Group II) fibers may occur, such that these fibers begin to take on nociceptive characteristics, specifically peptidergic function [19]. Animal model studies have demonstrated potent facilitation of the joint Group II afferents following induced joint inflammation [39] and induced monoarthritis

[40, 41]. Indirect evidence in patient populations may provide further support. Courtney et al. [34] demonstrated exaggerated FWR responses following active joint compression in patients with knee OA, and in a subsequent study, a pain-free anterior translatory stress applied to anterior cruciate deficit joint resulted in substantially increased reflex responses as compared to baseline [35]. Thus, afferent signaling from the articular tissues of the knee may be augmented, and spinal excitability maintained, with various forms of weight-bearing activities (standing, walking, pivoting). The consequence of constant nociceptive barrage at the OA joint with sustained central sensitization, is progressive expansion of pain and hypersensitivity [14].

Temporal Summation

Facilitated temporal summation is a feature of central sensitization, and is characteristic of many chronic musculoskeletal disorders including whiplash [42], fibromyalgia [43], and temporomandibular disorder [44]. Interestingly, experimentally induced delayed onset muscle soreness (DOMS) resulted in ipsilateral, but not contralateral, changes in temporal summation at 24 hours post-exercise [45], indicating that facilitation of this mechanism may occur more locally. Temporal summation is examined via repetitive stimulation utilizing a short interstimulus interval [46], and is typically induced using mechanical [47], electrical [48], or heat stimulus [44]. The increased FWR responses at these temporal delays are indicative of common mechanisms of wind-up in reduced preparations, namely persistent inward currents (i.e., plateau potentials) and modulatory actions of substance P [46], in which repeated stimulation at intervals<4–6 s progressively facilitates neuronal excitability. Facilitated temporal summation has been demonstrated in patient populations of knee OA [14], induced both at the knee and distally at the tibialis anterior. A significant correlation was also found between temporal summation and the patient's report of pain after walking, the peak pain in the previous 24 hours, and pain duration. These findings indicate the importance of central sensitization in the manifestation of knee OA pain.

Conditioned Pain Modulation

Tonic pain inhibition is characteristic of most pain-free individuals, although in some patient populations of chronic OA, conditioned pain modulation has been found to be deficient [14, 16••]. Conditioned pain modulation, previously referred to as diffuse noxious inhibitory control, is a pain inhibitory mechanism, mediated by the subnucleus reticularis dorsalis in the medulla [49]. In basic terms, application of a noxious stimulus at a remote site causes inhibition at the initial site of pain (e.g., the arthritic joint). This phenomenon has been studied extensively in laboratory studies and in relation to pharmacologic effects [50] and surgical [16••] management of pain. Descending serotonergic inhibition has been found to play a critical role in this pain inhibitory mechanism [51]. Lower serotonin (5-HT) gene-expression is characteristic of chronic pain [52], and it has been associated with aberrant conditioned pain modulation [53]. The clinical implications of this lack of nociceptive desensitization are significant, given that aberrant conditioned pain modulation has been suggested as a clinical predictor of chronic pain [54, 55••]. In chronic hip OA, conditioned pain modulation was found to normalize following extinction of the painful stimulus, via total joint arthroscopy [16••]. However, considering that up to 30 % of knee OA patients fail to gain pain relief with total knee arthroplasty [56], other factors in addition to impaired conditioned pain modulation are likely contributors.

Clinical Features of Chronic OA Pain

Altered Quantitative Sensory Testing

Hyperalgesia

The expansion of hyperalgesia, or pain sensitivity from the primary site of musculoskeletal insult to a regional or widespread hyperalgesia, is a hallmark of chronic pain. In knee OA, expansion of nociceptive receptive fields produces increased tenderness to palpation, both distal and proximal to the painful joint [14, 57]. The receptive field is the cutaneous area that, when stimulated, elicits a response from a single spinal neuron [58]. With receptive field expansion, there is a greater number of sensory afferents with input to the dorsal horn, leading to increased nociceptive information travelling to the spinal cord [59]. Clinically, the patient may describe a larger pattern of referred pain, with or without other sensory impairments. These sensory findings typically fail to correspond with a peripheral nerve or spinal nerve root pattern of distribution [60•]. Widespread hyperalgesia has been described in a number of conditions. including whiplash injury [61], irritable bowel syndrome [62], back pain [63], and pelvic pain [64]. By definition, fibromyalgia equates to chronic widespread pain, involving three or more segments of the body, plus the identification of at least 11 of the 18 designated tender points [65]. Assessment of hyperalgesia, via palpation and range of motion testing, is standard in the clinical setting; however, it has not always been quantified. Pressure pain threshold using algometry has been utilized to objectively measure hyperalgesia and to gain insight into the underlying mechanisms of chronic musculoskeletal pain [60•]. In general, measures of pressure pain threshold in patients with knee OA were found to be

diminished, indicating hyperalgesia, at the affected knee and at sites remote to the painful joint [14, 66, 67]. Thus, regional and/or widespread hyperalgesia is characteristic of chronic knee OA.

Hypoesthesia

Hypoesthesia to mechanical and vibration stimuli has been demonstrated concurrently with hyperalgesia [68–70]. Elevated vibrotactile thresholds have been found in patients with painful articular disorders [69, 70], as well as in experimental models of pain [71]. Both hypoesthesia and hyperalgesia may be triggered by nociceptive input, but are thought to be mediated by distinct neurophysiological mechanisms [72]. Both, however, are thought to be centrally mediated, either at spinal and/or supraspinal levels. Accordingly, Westermann et al. [73] demonstrated tactile hypoesthesia, but not hyperalgesia, on the contralateral joint in patients with osteoarthritis. Clinically, concurrent findings of hyperalgesia and hypoesthesia may make diagnosis more challenging and promote the use of vague diagnoses. While disconcerting as a finding in knee OA, the implications of pain-related hypoesthesia have been little studied. Vibratory deficits in patients with severe knee OA have been correlated to perceived instability during a step-over task [6]. In contrast, Shakoor et al. found no relationship observed between vibratory sense and symptomatic knee OA pain, but did find an association between greater somatosensory deficits and higher dynamic loads in OA, indicating the potential for greater impulsive loading of the joint, and thus, more rapid disease progression [74].

Thermal Sensation

While quantitative sensory testing of thermal detection is commonly studied in neuropathic pain [75], it has been less reported in OA patient populations. Musculoskeletal tissue (i.e., deep somatic tissue), show pronounced sensitization to mechanical stimuli in contrast to cutaneous nociceptors, which are particularly sensitized to thermal stimuli [76]. Thus, the finding of altered cutaneous thermal sensation in association with joint disease is intriguing and has led some researchers to propose that chronic musculoskeletal pain may be akin to neuropathic pain [77]. Few studies have reported on aberrant thermal sensation in the knee OA patient population; Wylde et al. [67] found thermal hypoaesthesia to both hot and cold stimuli at the affected knee, but not at a remote site.

Proprioception

Proprioception has been studied extensively in knee OA (see [5] for review). Early researchers proposed that joint disease likely damaged joint afferents contributing to proprioceptive deficits, and thereby facilitated movement dysfunction [78, 79]. However, subsequent studies recognized the significant role attributed to the muscle spindle in proprioception. Gandevia and McCloskey [80••] demonstrated that the ability to detect passive movement at a joint was not abolished when skin and joint receptors were anesthetized. Later research investigated the role of muscle impairment in proprioception deficits. Quadriceps weakness is a common impairment in knee OA, and has been associated with accelerated disease progression. [7]. Van der Esch [81] demonstrated that kinesthetic deficits (threshold to detection of passive movement) were associated with muscle weakness and functional deficits in knee OA patient populations. However, underlying mechanisms indicating a relationship between muscle performance and proprioceptive acuity have not been identified. Altered proprioceptive acuity may be another example of joint pain-related hypoesthesia; however, this has been little studied. Of interest, Swanik et al. [82] found that joint position sense, kinesthesia and balance all improved following total joint arthroplasty.

Neuromuscular Changes During Functional Activities

A major sequela of knee OA is the decline in functional ability reported by patients. It is estimated that 80 % of individuals with knee OA report some degree of movement limitation [83]. Perceived instability while performing activities of daily living has been reported as a component of this functional deficit [6, 84], yet was found to be unrelated to joint laxity or quadriceps strength [85]. Although it has been postulated that deficits in motor control lead to poor stabilization of the joint, causing microtrauma and pain [86], other models have proposed the converse, that pain alters neuromuscular control mechanisms critical for maintaining joint stabilization [87, 88], thereby leading to microtrauma and degeneration. Recent studies have begun to investigate this premise [3••, 89, 90].

Several studies have reported altered muscle activation patterns in persons with knee OA. Astephen [8] found that patients with severe radiographic OA changes demonstrated increased hamstring and gastrocnemius activation, but diminished rectus femoris activation during stance phase, with higher overall knee and hip flexion moments, when compared to healthy controls. Other studies have reported similar findings [91, 92], suggesting increased coactivation of musculature around the knee may function as a means to increase stability during ambulation. One potential consequence of this is altered joint loading, which may be a contributor to osteoarthritic progression [8, 92]. Less reported, however, is the interaction between mechanical features and patient symptoms. Further research that

addresses both neurophysiological and biomechanical factors is warranted.

Conclusion

Recent evidence suggests that musculoskeletal joint injury may result in altered nociceptive processing, including central sensitization and impaired descending pain modulation. The transition from nociceptive sensitization toward more chronic, widespread pain may occur due to repetitive musculoskeletal insult or an intense noxious event. Altered nociceptive mechanisms, including central sensitization and impaired descending pain modulation, are characteristic of chronic musculoskeletal pain, including osteoarthritis of the knee. Not addressed in this paper, but of critical importance, is the role of genetic predisposition and/or psychosocial factors that may facilitate central sensitization. Quantitative sensory testing measures may be useful in staging the evolution from acute to chronic musculoskeletal pain. Pressure pain threshold has been most commonly utilized, yet other measures may prove beneficial as well. Non-nociceptive sensory findings, such as hypoesthesia, may be associated with nociceptive sensitization. These sensory changes may have functional implications, yet further research is necessary before this may be established.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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