The Complexity of Pain around the Knee in Patients with Osteoarthritis

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ABSTRACT: Osteoarthritis of the knee is a common joint disease that can cause substantial pain and disability. The manifestation of pain, however, is highly variable and has a poor correlation to plain radiographs. The source of pain in gonarthrosis is elusive. Pain receptors have been found in the synovium, ligaments, capsule, subchondral bone and surrounding tissues with the exception of articular cartilage. The perception of pain is regulated at the spinal and cortical level and is often influenced by psychosocial conditions. There is no definitive treatment modality to relieve the pain and surgery does not necessarily guarantee improvement. Understanding and careful clinical assessment of the sore osteoarthritic knee together with better imaging such as magnetic resonance may improve treatment strategies.

KEY WORDS: osteoarthritis, knee, pain, total knee replacement, magnetic resonance imaging

EPIDEMIOLOGY

With the increase in life expectancy more people experience joint degeneration. Osteoarthritis is less common before age 40, but rises in frequency with age such that most people older than 70 have radiological evidence of osteoarthritis in some joints [4]. The knee is the major site of osteoarthritis [4,6]. The age- and gender-standardized incidence of osteoarthritis for the knee is 240 per 100,000 person-years [2]. Nearly half the patients with radiological features of osteoarthritis have no symptoms, and vice versa. The U.S. National Health and Nutrition Examination Survey identified the symptoms and signs of clinical osteoarthritis in 12% of 6913 people aged 25–74 years and found that X-ray evidence of osteoarthritis was present in at least one site in 33% [7].

MECHANISM

The degenerative process of the knee involves loss of hyaline articular cartilage, bony remodeling, bone marrow lesions, laxity of ligaments, capsular stretching, and weakness of periarticular muscles [8]. Often malalignment and further mechanical imbalance develop. These are accompanied by intermittent synovitis and local inflammation [9]. Irritation of the peristeum as a result of remodeling, denuded bone [10], effusion [11], bursitis [12] and spasm of surrounding muscles contribute to pain in osteoarthritis. Hyaline articular cartilage is unlikely to be a source of pain since it contains no nociceptive fibers. Obviously, osteoarthritic pain has multifaceted etiologies from within and outside the joint [13].

Pain around osteoarthritic knees can sometimes refer from a distant source (i.e., convergence pain) or derive from sympathetic efferent nerve-mediated pain due to faulty transmission at the spinal and cortical level in which it is regulated [14]. Moreover, pain is often influenced by psychosocial conditions [15]. The perception of knee pain is generated by peripheral nociceptive units comprising capillary, mast cell and nociceptor, which is sensitive to tissue damage [16].

The origin of joint pain is activated by noxious motion that stimulates A-δ mechanoreceptors and C-polymodal nerve endings in the synovium and surrounding structures with the exception of articular cartilage [13,17,18]. Most nociceptive-specific neurons that extend to the spinal cord have relatively
small receptor fields in the periphery. The other functional type of neuron that can produce pain is a wide dynamic range neuron that covers a wide territory of skin and joint [13]. Pain is transmitted through the spinal nerves and thalamus and is perceived by the somatosensory cortices [Figure 1].

The neuropeptide substance P, which is produced from non-myelinated sensory neurons in the synovium [19] and has been detected in both synovium and synovial fluid in osteoarthritis [20], may play a role in activating synovial and inflammatory cells and stimulates the secretion and potentiates the action of inflammatory mediators [17,19]. Substance P was also found in tissues of the peristeme, patellar fat pad, subchondral bone and joint capsule [21]. It was not demonstrated in the articular cartilage. In addition, probing different structures inside the knee in awake patients has shown that most pain-sensitive structures are located in the patellar fat pad, ligaments and synovium but not in articular cartilage [22].

Osteoarthritic pain has acute or chronic wax-and-wane characteristics. Acute pain is usually self-limiting and serves a protective biological function by acting as a warning of ongoing tissue damage. It is caused by stimulation of A-δ mechanoreceptors and C-polymodal pain receptors that are located in skin, bone, connective tissue and muscle. Chronic pain, on the other hand, serves no protective biological function. Rather than being the symptom of a disease process, chronic pain is itself a disease process. It is not self-limiting and can persist for years after the initial insult. Chronic pain can be refractory to multiple treatment modalities. If chronic pain is inadequately treated, associated symptoms can include chronic anxiety, fear, depression, sleeplessness, and impairment of social interaction.

The progression of nociception from an acute to a chronic process is not fully comprehended. Research in humans and animals suggests that peripheral mechanisms in acute pain and long-term potentiation of neuronal sensitivity to nociceptive inputs in the dorsal horn of the spinal cord may underlie the transition from an acute to a chronic process [23]. Chronic pain differs from the acute process not only in the duration of its course but also

### The manifestation of pain is highly variable with poor correlation to plain radiographs

In chronic pain, activation of N-methyl-D-aspartate receptors causes the release of substance P, which amplifies the pain by causing the spinal neurons carrying the signal to be easily stimulated. Elevated levels of substance P in spinal fluids have been documented in patients with osteoarthritis [24].

Pain at the knee can be referred from other sites such as the hip by a mechanism of bone and joint convergence pain. It happens when musculoskeletal afferent nociceptors converge on the same pain projection neurons (receptive field convergence) in the dorsal horn of the spinal cord, together with the superficial cutaneous afferent nerves supplying the painful area [25].

Infrequently, tissue injury causes sympathetic efferent nerve-mediated pain [25]. The cell damage releases several chemical mediators that sensitize peripheral nerve endings and cause primary hyperalgesia. Afferent pain signals intersect with other neurons in the spinal cord, resulting in efferent nerve reflexes and secondary sensitization of tissues in and around the area of injury.

Usually there is recovery from the nerve sensitization and pain followed by repair of the tissue damage; however, in some individuals pain can become persistent through activation of substance P intraneuronal transport. This is facilitated by the release of sympathomimetic amines and COX-2 up-regulation [26]. The sensitization of the dorsal horn cells of the spinal cord with substance P forms a closed loop pathway, referred to as sympathetic efferent nerve-mediated pain, which becomes self-sustaining.

Studies have tried to highlight certain pathologies inside the knee that may dominate in the generation of arthritic pain, such as articular synovitis, angiogenesis and torn menisci. Synovitis is recently gaining attention as an important feature in osteoarthritis [27]. As an innervated tissue, inflammation of the synovium may be a cause of pain. Synovial effusions have long been known as a feature of osteoarthritis. Some studies suggest that these effusions contribute to knee pain in osteoarthritis [28]. Substantive effusion distends the richly innervated capsule and causes pain. Angiogenesis may contribute to pain in osteoarthritis by enabling growth of new unmyelinated sensory nerves [29]. Angiogenesis and sensory nerves are seen in the synovium and at the osteochondral junction in osteoarthritis, penetrating into non-calcified articular cartilage and osteophytes. These perivascular unmyelinated nerve fibers containing substance P and calcitonin gene-related peptide are implicated in mediating the sustained burning pain described by patients with osteoarthritis [30]. Meniscectomy can lead to a reduction in pain [31], although mechanisms by which this occurs are yet to be elucidated. Myelinated and unmyelinated nerve fibers and free nerve endings have been localized in the meniscus with perivascular nerves containing substance P [32]. Blood vessels and nerves penetrate the outer portion of the normal human meniscus [33],

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**Figure 1.** Pathogenesis of pain in osteoarthritis of the knee

- Osteoarthritic knee
- Peripheral nociceptive unit
- Sympathetic efferent nerve-mediated pain
- Referred pain
- Inflammation
- Multilevel pathways
- Psychosocial conditions
- Inflammation
- Spinal nerves
- Thalamus
- Somatosensory cortices
reaching as far as its middle third, with the innermost portion remaining avascular and aneural.

**IMAGING IN PAINFUL OSTEOARTHRITIS OF THE KNEE**
The origin of pain in patients with radiographic osteoarthritis is not well understood. Definitive structural radiographic signs of osteoarthritis are associated with the risk of developing pain [34]; however, the simple model suggesting a linear relation between radiographic damage and pain is not supported by research findings. Approximately 25% of persons aged 55 or older have experienced knee pain on most days in a month in the previous year [4] and about half of them have radiographic osteoarthritis in the knee [Figure 2]; this latter group is considered to have symptomatic osteoarthritis. Less than 50% of people with evidence of osteoarthritis on plain radiographs have symptoms related to these findings [35]. Many without radiographic osteoarthritis of the knee probably have osteoarthritis that is not yet visible on radiography, an imaging procedure insensitive to early disease. The discrepancy between pain and radiographic features is probably because the origin of pain is multifactorial. Effusion, synovitis and bone marrow lesions are the principal findings associated with knee pain in magnetic resonance imaging and ultrasound studies of knee osteoarthritis. Wu et al. [36] used ultrasound to evaluate pain in patients with equal radiographic grades of osteoarthritis in both knees. They found medial compartment synovitis on ultrasound to be an important predictive factor of pain in patients with knee osteoarthritis. However, the factors that induce medial compartment synovitis were unclear.

**Understanding and careful clinical assessment together with better imaging such as magnetic resonance of the knee may improve treatment strategies**

The association of bone marrow lesion with osteoarthritis was identified only with the use of MRI to image joints [37] [Figure 3]. Bone marrow lesions can be a potential source of pain in osteoarthritis because they are localized in the subchondral bone and the subchondral bone is innervated [10]. Previous clinical investigations of bone marrow lesions as a source of pain in osteoarthritis have produced conflicting results. Some studies have shown an association with pain, especially when the lesions are large, while other authors questioned this relationship [38]. A recent systematic review examined the concurrent and predictive validity of MRI in bone marrow lesion as compared to symptoms, radiography, histology/pathology, arthroscopy, computed tomography, and alignment [39]. The relation of pain to bone marrow lesions, synovitis and effusion was moderate to strong, while the relation of pain to cartilage morphology or meniscal tears was weak or absent. The relation of cartilage morphology to radiographic osteoarthritis and radiographic joint space was inconsistent. There was a higher frequency of meniscal tears, synovitis and other features in persons with radiographic osteoarthritis. The presence of cartilage defects or bone marrow lesions is a potential predictor of total knee replacement.

**CLINICAL IMPLICATIONS**
A major objective in osteoarthritis treatment is to alleviate pain. Since the mechanism of pain in gonarthrosis is complex there are numerous non-surgical pain relief modalities – with variable success. An example of the ongoing research and development in this area is targeted biotherapy [40]. A phase III trial with an antibody raised against the nerve growth factor tanezumab was recently published, based on preclinical studies showing that NGF regulates the structure and function of responsive sensory neurons, including small-diameter nociceptive afferents. NGF appears to have a role in causing and augmenting pain in inflamed tissues.

*NGF = nerve growth factor*
There is still no definite effective treatment for osteoarthritis. Surgical options are implemented when conservative treatment fails; however, the results are not always satisfactory. For example, according to the U.S. National Health Institutes consensus statement [5], the success of primary total knee replacement in most patients is strongly supported by more than 20 years of follow-up data. Yet 15% are not satisfied with the results of surgery. Factors associated with the lack of improvement following surgery are not well known. The information accumulated so far regarding pain and its treatment in patients with evident osteoarthritis emphasizes the importance of accurate clinical diagnosis. A thorough description of the clinical evaluation of the knee is beyond the scope of this review; however, the clinician should differentiate between acute and chronic pain, try to identify its source and inquire about previous treatments. Equally important are the psychosocial condition of the patient, his or her medical history and the possibility of secondary gain. Surgery should be reserved for unresolved pain that is strongly correlated with the osteoarthritic process. This requires a thorough assessment.

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