The Complexity of Pain around the Knee in Patients with Osteoarthritis

Barak Haviv MD[1,2], Shlomo Bronak MD[1] and Rafael Thein MD[1,2]

[1]Arthroscopy and Sports Injuries Unit, Hasharon Hospital (Rabin Medical Center), Petah Tikva, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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.

IMAJ 2013; 15: 244–247

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

For Editorial see page 252

Osteoarthritis, a common joint disease [1,2], is a major source of pain and disability of the knee in the aging population [3,4]. It is characterized by loss of function and biochemical integrity of joint cartilage. The natural history of osteoarthritis of the knee is highly variable, with the disease improving in some patients, remaining stable, or gradually worsening in others. While the pain is often attributed to osteoarthritis, some of the pain experienced in and around the knee does not necessarily originate from it (i.e., referred pain). Moreover, there is a poor correlation of clinical symptoms with radiological appearance. Knee pain can sometimes persist even after surgery. Although symptomatic patients with advanced osteoarthritis can benefit from knee replacement surgery, about 15% continue to experience pain despite an uneventful perioperative history and unremarkable postoperative imaging [5]. This article reviews the current literature regarding the source and mechanism of pain around the osteoarthritic knee.

The mechanism of pain in patients with gonarthrosis is multifaceted

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 periosteum 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 periosteum, 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 manifestation of pain is highly variable with poor correlation to plain radiographs

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 underline 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 in the different receptors involved in the mechanisms of action. 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].

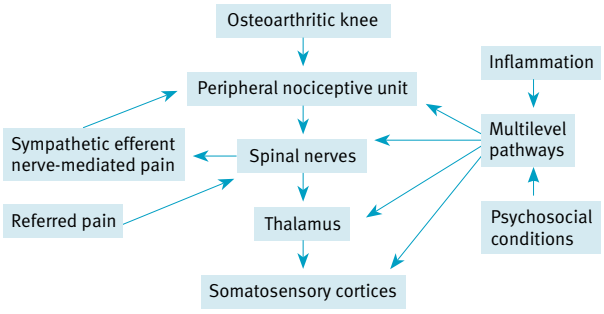
Pain at the knee can be referred from other sites such as the hip by a mechanism of bone and joint convergence pain. It happens when musculoskeletal afferent nociceptors converge on the same pain projection neurons (receptive field convergence) in the dorsal horn of the spinal cord, together with the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

Figure 1. Pathogenesis of pain in osteoarthritis of the knee



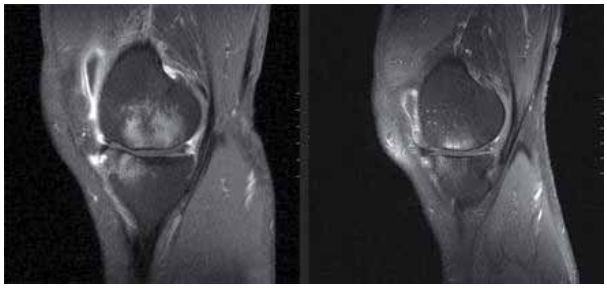
reaching as far as its middle third, with the innermost portion remaining avascular and aneural.

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.

Figure 2. Radiograph of osteoarthritic knee, an anterior posterior view

Figure 3. Magnetic resonance imaging of osteoarthritic knee showing bone marrow lesion, a sagittal view



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.

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

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.

Corresponding author:
Dr. B. Haviv
Arthroscopy and Sports Injuries Unit, Hasharon Hospital, Petah Tikva 49372, Israel
Phone: (972-3) 937-2750, **Fax:** (972-3) 937-2751
email: barak_haviv69@hotmail.com

References

1. Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol* 2006; 20: 3-25.
2. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum* 1995; 38: 1134-41.
3. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994; 84: 351-8.
4. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001; 60: 91-7.
5. NIH Consensus Statement on Total Knee Replacement. *NIH Consens State Sci Statements* 2003; 20: 1-32.
6. Felson DT. Clinical practice. Osteoarthritis of the knee. *N Engl J Med* 2006; 354: 841-8.
7. Lawrence, RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1988; 41: 778-99.
8. Felson DT, McLaughlin S, Goggins J, et al. Bone marrow edema and its relation to progression of knee steoarthritis. *Ann Intern Med* 2003; 139: 330-6.
9. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum* 2001; 44: 1237-47.
10. Felson DT, Chaisson CE, Hill CL, et al. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* 2001; 134: 541-9.
11. Hill CL, Gale DR, Chaisson CE, et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. *J Rheumatol* 2001; 28: 1330-7.
12. Hill CL, Gale DR, Chaisson CE, et al. Periarticular lesions detected on magnetic resonance imaging: prevalence in knees with and without knee symptoms. *Arthritis Rheum* 2003; 48: 2836-44.
13. Felson DT. The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol* 2005; 17: 624-8.
14. Forrest JB. Pathophysiology of acute pain. In: Acute Pain: Pathophysiology and Treatment. Grimsby, ON: Manticore, 1998: 31-65.
15. Geenen R, Bijlsma JW. Psychological management of osteoarthritic pain. *Osteoarthritis Cartilage* 2010; 18: 873-5.
16. Ganong WF. Review of Medical Physiology. 20th edn. New York: McGraw-Hill Companies Inc., 2001.
17. Buchanan WW, Kean WF. Osteoarthritis: II. Pathology and pathogenesis. *Inflammopharmacology* 2002; 10: 19-48.
18. Wyke B. The neurology of joints: a review of general principles. *Clin Rheum Dis* 198; 57: 233-9.
19. Pelletier JP, Caron JP, Evans C, et al. In vivo suppression of early experimental osteoarthritis by interleukin-1 receptor antagonist using gene therapy. *Arthritis Rheum* 1997; 40: 1012-19.
20. Menkes CJ, Renaux M, Laoussadi S, et al. Substance P levels in the synovium and synovial fluid from patients with rheumatoid arthritis and osteoarthritis. *J Rheumatol* 1993; 20: 714-17.
21. Wojtys EM, Beamann DN, Glover RA, et al. Innervation of the human knee joint by substance-P fibers. *Arthroscopy* 1990; 6: 254-63.
22. Kellgren JH, Samuel EP. The sensitivity and innervation of the articular capsule. *J Bone Joint Surg Br* 1950; 32: 84-92.
23. Klein T, Magerl W, Hopf HC, et al. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci* 2004; 24: 964-71.
24. Lindh C, Liu Z, Lyrena S, et al. Elevated cerebrospinal substance P-like immunoreactivity in patients with painful osteoarthritis, but not in patients with rhizopatic pain from a herniated lumbar disc. *Scand J Rheumatol* 1997; 26: 468-72.
25. Konttinen YT, Kemppinen P, Segerberg M, et al. Peripheral and spinal neural mechanisms in arthritis, with particular reference to treatment of inflammation and pain. *Arthritis Rheum* 1994; 37: 965-82.
26. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001; 344: 907-16.
27. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone* 2012; 51: 249-57.
28. Torres L, Dunlop DD, Peterfy C, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis Cartilage* 2006; 14: 1033-40.
29. Ashraf S, Walsh DA. Angiogenesis in osteoarthritis. *Curr Opin Rheumatol* 2008; 20: 573-80.
30. Dieppe PA. Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005; 365: 9-73.
31. Roos EM, Ostenberg A, Roos H, Ekdahl C, Lohmander LS. Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. *Osteoarthritis Cartilage* 2001; 9: 316-24.
32. Assimakopoulos AP, Katonis PG, Agapitos MV, et al. The innervation of the human meniscus. *Clin Orthop Relat Res* 1992; 275: 232-6.
33. Danzig L, Resnick D, Gonsalves M, et al. Blood supply to the normal and abnormal menisci of the human knee. *Clin Orthop Relat Res* 1983; 172: 271-6.
34. Sellam J, Herrero-Beaumont G, Berenbaum F. Osteoarthritis: pathogenesis, clinical aspects and diagnosis. In: Bijlsma JWJ, Burmeister GR, Da Silva JAP, Faarvang KL, Hachulla E, Mariette X, eds. EULAR Compendium on Rheumatic Diseases. London: BMJ Publishing Group, 2009: 444-63.
35. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol* 2000; 27: 1513-17.
36. Wu PT, Shao CJ, Wu KC, et al. Pain in patients with equal radiographic grades of osteoarthritis in both knees: the value of gray scale ultrasound. *Osteoarthritis Cartilage* 2012; 20: 1507-13.
37. Lo GH, McAlindon TE, Niu J, et al; OAI Investigators Group. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2009; 17: 1562-9.
38. Kornaat PR, Bloem JL, Ceulemans RY, et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. *Radiology* 2006; 239: 811-17.
39. Hunter DJ, Zhang W, Conaghan P, et al. Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. *Osteoarthritis Cartilage* 2011; 19: 557-88.
40. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind placebo-controlled phase III trial. *J Pain* 2012; 13:790-8.