

## GENESIS OF PAIN IN ARTHROSIS

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**ABSTRACT**

Advances in knowledge regarding the pathophysiology of pain among patients with knee osteoarthritis suggest that the central nervous system is involved as a source that maintains and amplifies the painful condition such that it is refractory to conventional orthopedic and rheumatological treatment. Initially, hyperalgesia is observed only at the affected site. However, when the pain becomes refractory, peripheral and central sensitization mechanisms contribute towards maintaining and amplifying the painful conditions, regardless of the peripheral process that originated the pain. At this stage, even removal of the etiological agent may no longer be enough to relieve the painful symptoms. It then becomes necessary to envisage that other factors, distant from the affected joint, may be responsible for the

disabling painful condition in such patients. At present, osteoarthritis does not have any known cure, and the aim of treatment is to lessen the pain while improving function and health-related quality of life, and whenever possible, to minimize the toxicity of the therapy. In the light of emerging evidence suggesting that the central nervous system has a role in the physiopathology of pain in patients with knee arthrosis, the central nervous system should be taken into consideration as a therapeutic target, instead of only administering local treatment using ordinary analgesics, anti-inflammatory drugs and non-pharmacological measures. Thus, methods that modulate the spinal cord and cerebral cortex, including the use of antidepressants, may have a role in managing these patients.

**Keywords** – Arthrosis; Knee/physiopathology; Pain/therapy

**INTRODUCTION**

Osteoarthritis is the most prevalent joint disease and is the main cause of functional incapacity<sup>(1,2)</sup> among elderly people<sup>(3)</sup>. Knee osteoarthritis is the fourth commonest cause of health problems among elderly women<sup>(4)</sup>. The risk of incapacity consequent to osteoarthritis alone is greater than from any other medical condition<sup>(3)</sup>. Currently, there is no known cure for osteoarthritis, and the aim of treatment is to improve pain, function and health-related quality of life, while minimizing the toxicity of the therapy whenever possible<sup>(3)</sup>.

Osteoarthritis is defined as failure of the joint cartilage resulting from mechanical, genetic, hormonal,

bone and metabolic factors, which gives rise to an imbalance between the degradation and synthesis of joint cartilage and subchondral bone. It is manifested by morphological, biochemical, molecular and biomechanical abnormalities of cells and the extracellular matrix, which lead to softening, fibrillation, ulceration and loss of the joint cartilage, and to sclerosis of the subchondral bone and formation of osteophytes and subchondral cysts.

**PHYSIOPATHOLOGY**

Despite deep knowledge of the physiopathology of arthrosis at molecular level, there is still little knowledge about the genesis of pain in such patients.

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Classically, it is known that the possible causes of pain in arthrosis are related to increased intraosseous pressure due to vascular congestion of the subchondral bone, growth of osteophytes, synovitis and inflammation, capsular fibrosis, contracture and muscle weakness.

In a previous study, we showed that hyperalgesia of central origin was responsible for 61% of the pain reported by such patients on self-assessment scales like the visual analogue pain scale, WOMAC (Western Ontario McMaster Osteoarthritis Index) and SF-36 (Medical Outcomes Study 36-item Short Form Health Survey)<sup>(5)</sup>. This suggests that both the central nervous system and the peripheral system are probably involved in maintaining the state of chronic pain in these patients. It seems that initially, hypersensitivity is only observed at the site affected. However, when the pain becomes refractory, mechanisms for central and peripheral sensitization start to contribute towards maintaining painful conditions, independent of the peripheral process that originated the pain.

Differently from acute pain, for which the physiopathology is relatively well known and the therapeutic results are more encouraging, chronic pain does not translate the magnitude of the tissue lesion and treatments remain unsatisfactory. Recently, development of new diagnostic methods for clinical investigation of central sensitization has furnished new knowledge for better understanding of the physiopathology of chronic pain. This new information has demonstrated that functional abnormalities in the central and peripheral nervous systems may play an important role in maintaining chronic pain.

Better comprehension of the complex mechanisms involved in generating, modulating, amplifying and perpetuating pain has an important role in determining the best therapeutic regimen to use in treating patients with knee arthrosis. Modern treatment for pain, for example, is no longer based solely on symptom relief but on controlling it based on the physiopathological mechanisms involved<sup>(6)</sup>.

Recently, it was observed that intense and persistent nociceptive stimuli coming from peripheral tissues could trigger neuroplastic abnormalities in the central nervous system<sup>(7,8)</sup>. These abnormalities include increased excitability of the neurons in the posterior horn of the spinal cord, thus producing

hyperalgesia, temporal summation of the pain and ascending regulation.

These neurochemical changes suggest that the pain induces and is partially maintained by a state of central sensitization<sup>(9)</sup>, in which increased transmission of nociceptive information allows neurons that are not normally involved in transmitting pain information to start to do so. In this way, stimuli such as pressure on certain parts of the body, which in healthy volunteers are not interpreted as painful, start to be perceived as such<sup>(5)</sup>. It is worth emphasizing that peripheral nociceptive stimuli may begin and maintain the state of central sensitization, as has already been described in relation to fibromyalgia<sup>(7,10-12)</sup>.

Although chronic painful symptoms are subjective by nature, they may correlate with neuroimaging evidence that reveals increased levels of cerebral activation responses<sup>(13-15)</sup>.

Several authors have already demonstrated that central sensitization may be involved in the genesis, maintenance, amplification and exacerbation of painful symptoms in patients with arthrosis in various body segments<sup>(15-19)</sup>. Like in our study (Imamura et al<sup>(5)</sup>), cutaneous and deep hyperalgesia has been observed in the forearms of patients with rhizarthrosis<sup>(17)</sup> and in the anterior tibial muscle of patients with knee arthrosis<sup>(19)</sup>.

It is interesting to note that painful sites with lower tolerance of pressure present high levels of substance P, calcitonin, bradykinin, tumor necrosis factor, interleukin-1, serotonin and norepinephrine, in comparison with healthy individuals without spontaneous pain or asymptomatic subjects<sup>(20)</sup>. In individuals with spontaneous pain, areas distant from the painful site also demonstrate significant increases in the levels of these chemical mediators<sup>(21)</sup>.

It is known that these abnormalities occur not only in the spinal cord<sup>(22)</sup>, but also in other structures of the central nervous system. For example, a pilot study has already revealed that areas of the brain were involved in pain processing in a group of 12 patients with knee osteoarthritis<sup>(23)</sup>. The results showed that the arthritis pain was associated with increased activity in the cingulate cortex, thalamus and amygdale, which are areas involved in processing the emotional aspects of pain<sup>(23)</sup>.

The presence of peripheral and central sensitization

in patients with chronic pain induces additional neuroplastic changes in the posterior horn of the spinal cord and in cortical areas that then maintain and amplify the painful state, thus forming a vicious circle with refractory symptoms. At this stage, even removal of the etiological agent may no longer be enough to relieve the painful symptoms. It therefore becomes necessary to consider that other factors, distant from the joint that is affected, may be the agents responsible for the painful and incapacitating symptoms in these patients<sup>(5,24)</sup>, not only at the originating point<sup>(24)</sup>, but also for central sensitization<sup>(5)</sup>.

### **WARNING SIGNS FOR THE DIAGNOSIS OF PAIN IN KNEE ARTHROSIS: PHYSICAL EXAMINATION TIPS FOR ORTHOPEDISTS**

Within this context, diagnosing peripheral and central sensitization is very important<sup>(25,26)</sup>, because when this is present, it means that neurons of the posterior horn of the spinal cord that would normally only be activated by nociceptive stimuli can now be activated by other stimuli, including non-nociceptive stimuli. This phenomenon is widely known as allodynia<sup>(27)</sup>. This explains why, in cases in which central sensitization has become established, minimal peripheral stimuli are sufficient to maintain the painful and incapacitating condition<sup>(8)</sup>.

Warning signs are clinical indicators of problems that are more serious and which require greater medical attention. These signs were developed for use in cases of acute lumbalgia. However the same concepts can be applied in a more wide-ranging manner in searching for pain centers or localized hyperalgesia that has disseminated to parts of the body other than the knee region, and for increases in the size of painful areas. For example, the pressure needed to cause pain, applied to various parts of the body, is lower among these patients than among normal controls of the same gender and age<sup>(5)</sup>. With sensitization of the localized pain areas and bombardment of the central nervous system with neuron impulses, the adjacent segments start to become progressively sensitized. One important finding is that the degree of increase in sensitization correlates with the pain level.

## **PAIN MANAGEMENT**

In the light of this emerging evidence suggesting that the central nervous system has a role in the pathophysiology of pain among patients with knee arthrosis, the structures of the central nervous system should also be considered to be therapeutic targets, instead of administering purely local treatment with common analgesics, anti-inflammatory agents and non-pharmacological measures.

We often see patients who, despite undergoing correct orthopedic treatment, persistently present painful symptoms. These symptoms are generally segmental pains along the thigh and lower leg.

To understand these symptoms, we studied<sup>(5)</sup> occurrences of segmental pain in the region of the vastus medialis, long adductor, anterior tibial and peroneus longus muscles that was associated with cutaneous hyperalgesia in these regions, among 62 patients with knee osteoarthritis who were awaiting treatment consisting of total arthroplasty. We found that these symptoms occurred more frequently among these patients than among 22 patients of the same sex and age who had not had any painful symptoms in the lower limbs for the past year ( $p < 0.001$ ).

There is radiological evidence that persistent pain leads to atrophy of the cerebral cortex, and that this improves with adequate treatment for this pain. If the participation of the central nervous system in the genesis of chronic pain like the pain caused by knee arthrosis is neglected, a mechanism that might explain the persistent pain seen in up to 60% of such patients will remain unknown.

The use of physiotherapeutic means and centrally acting drugs such as antidepressants<sup>(28)</sup> needs to be taken into consideration in treating these patients.

## **FINAL REMARKS**

In analyzing the pain presented by patients with knee arthrosis, which is pain that evolves chronically and is refractory to the usual orthopedic treatment, significant changes in cortical areas that are associated with affective and emotional processing need to be taken into consideration.

Among these patients, it is of fundamental importance to reduce or even to prevent amplification of the symptoms caused by continual activation of these areas.

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