Pathogenesis and clinical aspects of pain in patients with osteoporosis

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Summary

Bone pain is one of the most frequent kinds of chronic pain, mainly in elderly patients. It causes a significant worsening of functional capacity and deterioration in the quality of life in people affected. Mechanisms of pain in osteoporosis are poorly known and often extrapolated by other pathologies or other experimental model. One of principal causes would be a “hyper-remodeling” of bone, that involves osteoclasts activity and pathological modifications of bone innervation. Several studies show that osteoclasts play a significant role in bone pain etiology.

Pain in osteoporosis is mainly nociceptive, if it become persistent a sensitization of peripheral and central nervous system can occur, so underlining the transition to a chronic pain syndrome. Central sensitization mechanisms are complex and involve several neuromediators and receptors (Substance P, NMDA, etc.).

Most common manifestations of osteoporosis are vertebral compression fractures that cause persistent pain, though to differentiate from pain originating in structures as joint or muscle. First manifestation can be an acute pain due to pathological fracture, those of hip often causes disability.

Pain in osteoporosis is an important clinical challenge. Often its complications and consequences on patient quality of life are underestimated with not negligible social implications.

A balanced and early multimodal pain therapy including opioids as necessary, even in cases of acute pain, improve the functional capacity of patients and helps to prevent neurological alterations that seems to contribute in significant way in causing irreversible pain chronic syndromes.

Bone innervation

For a long time, bone has been considered a structure that escapes the nervous regulation, today we knows that it is a widely innervated tissue and that important nociceptive no-adrenergic and peptidergic innervation play a role in maintaining homeostasis as well as in determining pathological situations.

The innervation sense noxious stimuli and transmit the information to the spinal cord and brain, moreover it could play a chronic pain syndrome. Central sensitization mechanism, defined by IASP as “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” (4). This sensitization can significantly contribute to clinical manifestation of osteoporotic pain and to its chronicization (5, 6). We can deduct that pain is a multidimensional experience; its intensity is influenced by nociceptive, neurological, emotional, social and other components that contribute to create the “pain experience”. Evaluating a patient that complaint of bone pain, all these factors must be considered to find a good strategy of care.

Mechanisms of pain in osteoporosis are poorly known and often extrapolated by other pathologies or other experimental model. One of principal causes of pain in metabolic disease would be a “hyper-remodeling” of bone that involves also osteoclasts activity and modification of bone innervation. It has been demonstrated that treatments that inhibit this bone remodelling have an analgesic effect (7-9). Jakob et al. shown a reduction in back pain and improvements in quality of life during treatment with teriparatide. The improvement was still evident 18 months after discontinuation of the drug, so osteoclasts activity and modification of bone innervation.

Pain in osteoporosis is one of the most frequent kinds of chronic pain, mainly in elderly patients. It can cause a significant worsening of functional capacity and deterioration in the quality of life of people affected.

By a survey, carried out on a sample of 46,000 people across Europe, results that 19% of European adults suffers from moderate to severe chronic pain of degenerative origin. In Italy, this percentage is raised to 26%. Pain is often caused by osteoarthritis, but a high percentage of interviewed people reported bone pain as consequence of metabolic disorders (1).

The predominant metabolic disease causing pain is osteoporosis; it is estimated that 30% of women over the age of 65 years suffers from osteoporosis and is at risk of vertebral fracture, follow osteomalacia and Paget’s disease (2).

According to International Association of Study on Pain (IASP) chronic pain is “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (3). The most frequent and earlier complication of intense pain is “central sensitization”, defined by IASP as “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” (4).

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an important role in the regulation of physiological phenomena as the local blood flow and bone remodeling (11, 12).

Know features and functions of the sensory and sympathetic innervation of bone should provide a better understanding of the mechanisms that generate and maintain bone pain and aid in developing therapeutic strategies for treating it (13).

It is demonstrated that, whereas bone mass and strength decline with age, density of sensory nerve fibers in the tissue, do not decline in older age (14).

Bone is primarily innervated by thinly myelinated sensory nerve fibers (A-delta) and peptide-rich CGRP+ nerve fibers. These nerve fibers may express the high affinity nerve growth factor (NGF) receptors Trk A, which mediate the multiple effects of Nerve Growth Factor, including neuronal differentiation and survival. That pattern of innervation is present in the periosteum, mineralized bone, and marrow (15, 16).

Julius and Basbaum shown that subsets of sensory neurons express different acid-sensing ion channels. Two acid-sensing ion channels expressed by nociceptors are the transient receptor potential vanilloid 1 (TRPV1) and the acid-sensing ion channel-3 (ASIC-3). Both of these channels are excited and sensitized by a decrease in pH (17). Decrease of pH in the bone always happens during osteoclasts hyperactivity.

Recently, it has been shown that when osteosarcoma cells grow within the bone, there is a remarkable and ectopic sprouting and formation of neuroma-like structures by sensory and sympathetic nerve fibers. An anti-NFG therapy blocks the sensory and sympathetic nerve fibers pathological sprouting and formation of neuroma-like structures, therefore attenuates the generation and maintenance of cancer pain in this model. These reports suggest that following injury or disease of the skeleton, significant sprouting of TrkA+ nerve fibers can occur, and it appears that endogenous stromal cells as well as inflammatory and immune cells can produce NGF causing pathological alteration of bone innervations (18-20).

So, we have sensory nerve fibers expressing nociceptors sensitized by lowering of pH, whose density do not decline in old bone, moreover, during pathological processes of bone, sensory nerve fibers undergo pathological modifications. All of these factors contribute to generate and maintain pain.

Osteoclasts activity and pain

In healthy bone, balance between osteoblastic and osteoclastic activity is under the control of many local and general factors: citicoline (interleukin 1, TNFa, interferon γ), hormones (vitamin D, parathyroid hormone, calcitonin, thyroid hormones, oestrogens, androgens), prostaglandins, etc. Following an imbalance of these factors, as demonstrated during metabolic diseases but also in cancer, an excessive osteoclastic activity can occur. Bone disorders with increased osteoclastic bone resorption such as metastatic bone disease, Paget’s disease, osteoporosis, fibrous dysplasia and osteogenesis imperfecta are frequently associated with pain (21).

Although the literature does not give definite indications about the role of osteoclasts in the generation of pain during metabolic diseases, several studies regarding bone cancer pain show that these cells play a significant role in its etiology (22).

Osteoclasts degrade bone minerals by secreting protons through the vacuolar H+-ATPase, creating acidic microenvironments. Using an animal model, stimulating osteoclasts activity with a single subcutaneous injection of the complete Freund’s adjuvant (CFA) in the hind-paw and subsequently suppressing the activity by the bisphosphonates, zoledronic acid and alendronate and osteoprotegerin, Nagae et al. concluded that osteoclasts play an important role in CFA-induced inflammatory pain through and activation of the acid-sensing receptors including ASICs and TRPV1 by creating acidosis (21).

Bone pain chronicization

Nociceptive pain, peripheral neuropathic pain, but also central sensitization pain have been suggested as clinically meaningful mechanisms in generating musculoskeletal pain (5).

Nociceptor inputs can trigger a prolonged increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, this event could lead to a central sensitization that results in secondary changes in brain activity that can be detected by electrophysiological or imaging techniques. The typical manifestations of such a complex mechanism are: pain hypersensitivity, dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, afferentations, and enhanced temporal summation.

Studies in clinical cohorts reveal changes in pain sensitivity that have been interpreted as result of an important contribution of central sensitization to the pain phenotype in patients with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and postsurgical pain. The presence of those pain hypersensitivity syndromes in the absence of inflammation or neural lesions, their similar pattern of clinical presentation and response to centrally acting analgesics, may reflect a common path of central sensitization to their pathophysiology (23).

This mechanism involves activation of N-methyl-D-aspartate receptors, release of substance P, which amplifies pain by causing the spinal neurons to be easily stimulated (6). Also spinal glial activation is now considered an important component in the development and maintenance of central sensitization (24):

- The microglia seems to respond to a range of pathological conditions such as ischemia, infection and mechanical insults, modifying itself in such a way that the risk of complicating pain with a neuropathic component is increased.
- The release of proinflammatory mediators leads to an activation of glia, which tends to self-renew and causes excessive stimulation of the spinal cord gray matter, producing sensory disturbances typical of the neurological damage.

Repair of the tissue damage can be followed by a recovery from the nerve sensitization and pain.

If peripheral sensitization and neuronal sensitivity long-term potentiation in the dorsal horn of the spinal cord occur, it is very likely the transition from an acute to a chronic process.

Pain assessment

A correct approach to the patient suffering of pain includes an adequate pain assessment. It is necessary to evaluate different components of the “pain experience”, such as:
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a. etiology
b. interaction between the sensory and psychological component
c. patient’s functional status
d. response to analgesic and etiologic therapies
e. tolerance to drugs, history of addicted personality or drugs abuse
f. characteristics of pain (type, distribution, quality, intensity and duration).

Moreover, it is necessary to measure pain intensity. This measurement, carried out periodically, allows to evaluate the effectiveness of therapeutic intervention and patient compliance.

Many tools are available for pain assessment. Some are useful to assess principally the sensory component of pain, as unidimensional tools like “Visual Analog Score or Numeric Rate Scale”.

To evaluate multidimensional components of pain and its impact on patient behaviour, his daily activities we need to use multidimensional tools that analyze all aspects of the “pain experience”, the best known are: Mc Gill Pain questionnaire or the easier Brief Pain Inventory.

In elderly people with impaired cognitive function always exists the risk to underestimate and undertreat pain (25).

Clinical aspects

Unfortunately, osteoporosis often causes few symptoms for a long time, it has been called the “silent thief” because it steals for years calcium from our bone and then manifests with acute pain caused by pathologic fractures.

Chronic mild bone pain, caused by described mechanisms, has clinical features that make differential diagnosis difficult respect to pain from other structures as joint or muscles.

The most frequent painful manifestation of osteoporosis is vertebral compression fractures of the spine, most of cases in thoraco-lumbar tract (26, 27).

Compression fractures of vertebral bodies are particularly worrisome. It has been hypothesized that fractures occur because of an increased load on the spine cause by contraction of paraspinal muscles (28).

Those fractures usually have an insidious onset and may produce only low-grade back pain, infrequently associated to neurologic deficits, but pain can also be sudden and severe, especially in the lower back, so that movements are difficult or impossible.

Over time, multiple fractures may lead to progressive loss of stature and continuous contraction of the paraspinal musculature to maintain posture. This combination of events results in fatigued muscles and pain that may continue even after the original compression fractures have healed (29).

Other complications of compression fractures include constipation, bowel obstruction, prolonged inactivity, deep vein thrombosis, increased osteoporosis, progressive muscle weakness, loss of independence, kyphosis and decreased height, crowding of internal organs, respiratory disturbances, low self-esteem, emotional and social problems.

With one segment collapsed there is a point of instability and the adjacent levels have to support the additional load. This increased strain on the adjacent segments may result in degeneration of the spine and additional pain (30) with further worsening of patient quality of life.

Other painful fractures are really frequent in hip and knee and can cause chronic pain and disability. Painful chronic syndromes can be also happen after arthroplasty, Piscitelli et al. reported that pain level and function impairment before surgical intervention, along with other factors, play an important role in causing persistent pain after joint arthroplasty (31).

Some considerations about prevention and therapies

Adequate prevention and adequate analgesic therapy are able to ensure a better quality of life for these patients, also reducing social and economic consequences of painful osteoporosis.

Literature is unanimous in supporting the role of physical exercise in the prevention of chronic pain of osteo-articular origin; in particular there is strong evidence for a beneficial effect of exercise on the pathogenesis of osteoporosis (32).

Drugs mainly used in osteoporosis are bisphosphonate and other drugs that can prevent and reduce pain acting on osteoclasts activity. Nowadays is essential to use weak and strong opioids in the treatment of severe and persistent pain caused by osteoporosis. That’s also because in inflamed tissues the interaction between opioids derived from leukocytes and opioid receptors can contribute to a potent and clinically relevant inhibition of pain (33).

On the other hand, we have also to consider as an emerging problem, that high doses of opioids, administered in persons aged 60 years and older, for chronic non-cancer pain can be associated with an increased risk of fracture confirmed by medical record review (34).

Conclusion

Pain in osteoporosis is an important clinical challenge; its mechanisms are complex and not completely understood.

Often its complications and consequences on patient quality of life are underestimated and with not negligible social implications.

A balanced and early multimodal pain therapy including opioids as necessary, even in cases of acute pain, improves the functional capacity of patients and helps to prevent neurological alterations that seem to contribute in significant way in causing irreversible pain chronic syndromes.

References