Literature Review

Osteogenic Pain: A "Novel" Concept Based on Rodent and Human Studies

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Background: The chronic bone pain associated with various skeletal conditions poses significant challenges to clinical management. Current treatments, which often rely on systemic opioids, come with adverse effects, emphasizing the need for safer alternatives. Understanding the neurobiology of bone pain and exploring novel therapeutic avenues for the condition are critical for improving patient outcomes.

Objectives: This review aims to examine recent preclinical studies elucidating the mechanisms underlying bone pain and to propose an innovative concept, known herein as osteogenic pain, to aid in relieving it.

Study Design: A comprehensive review of preclinical studies investigating bone pain mechanisms and treatment approaches was conducted. Literature focusing on the interaction between neurons and bone microenvironment cells was examined, as was literature concerning the development of nonopioid analgesics targeting peripheral processes.

Results: This review highlights the intricate interactions among neurons, immune cells, osteoclasts, and osteoblasts within the bone microenvironment that contribute to the pathophysiology of bone pain. The study identifies the increased excitability of primary afferent neurons as a crucial factor in bone pain development, and a new concept of osteogenic pain is proposed.

Limitations: The translation of preclinical findings to clinical settings requires further validation, highlighting the need for more clinically relevant animal models and experimental methods.

Conclusion: The proposal of "osteogenic pain" as a new concept underscores the need for improved clinical methods of treating bone pain and validated tools for the assessment and diagnosis thereof. The future of bone pain management lies in exploration, including targeting peripheral processes and leveraging innovative therapies, interventional techniques, and inclusive integration of artificial intelligence into them. Through new tools for assessment and monitoring, these efforts may provide patients who have bone disorders with better pain relief and improved quality of life.

Key words: Chronic pain, osteoporosis, cancer pain, osteoarthiritis, bone cancer pain, physiopathology

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Malignant and nonmalignant skeletal diseases associated with acute and chronic bone pain are highly prevalent, and bone pain exerts a negative impact on patients' physical ability and quality of life as well as imposing social medical costs. Despite these factors, the mechanisms

of bone pain are poorly understood (1). A wide variety of skeletal conditions can cause bone pain, including inflammation, trauma, infections, autoimmune diseases, genetic disorders, degenerative diseases, cancer, and metastasis. The presence of metastases in the bone, which is the third most common metastatic site, predicts the development of pain and is the most common cause of cancer-related pain (2,3). Bone pain is not exclusive to patients with bone cancer. Worldwide, 9.6% of men and 18.0% of women older than 60 years suffer from bone pain caused by symptomatic osteoarthritis (OA) (4). In addition, up to 30% of postmenopausal Caucasian women in the United States have osteoporosis, increasing their risk of painful osteoporotic fractures (5). These fractures are associated with reduced functional status and more admissions to nursing homes and rehabilitation hospitals. Thus, skeletal pathologies and the associated risk of developing pain will continue to put an increasing medical and economic load on both individuals and society (6).

Methods

Objective

This review aims to examine recent preclinical studies elucidating the mechanisms underlying bone pain and to propose an innovative related concept, known here as osteogenic pain. The study also reviews the pathophysiological mechanisms of bone pain.

Study Design

A comprehensive review of preclinical studies investigating bone pain mechanisms and treatment approaches was conducted.

We conducted a wide-ranging literature review that addressed the mechanisms and pathophysiology of bone pain and major bone conditions.

Search Strategy

The following search engines and electronic databases were accessed for articles published up to June 2024: MEDLINE (accessed via PubMed), Embase, and Google Scholar. The Boolean operators and MeSH terms used in the searches were as follows: cancer pain; neoplasm-related pain; osteoporosis; bone cancer pain; bone resorption; myeloid-derived suppressor cells; nociceptive; bone; NGF; TrkA; aging; neuropathic; long bones; osteoplasty; tumors.

Results

Cumulative evidence suggests that bone tissue may be a direct source of pain. Bone pain can be perceived if the periosteum, cortical bone, or bone marrow are disturbed, injured, or affected by pathological processes (7,9). Patients with fractures involving the cortical bone and periosteum often experience sharp and localized pain, while patients with bone marrow tumors experience a constant dull pain that increases as the disease progresses (3,7,9). Almost a century ago, clinicians first demonstrated that the injection of physiological saline under pressure into the canine bone marrow resulted in violent pain reflexes (10). Likewise, seminal studies conducted in 1944 reported that direct mechanical stimulation of the periosteum in waking humans, including the authors, elicited an immediate sharp, arresting pain. Furthermore, they documented that the periosteum possessed a significantly lower threshold than did the stimulated ligaments, fibrous capsule of the joints, tendons, fascia, or muscle (11). In support of these functional studies, it has been shown that not only periosteum but also bone marrow and cortical bone from dogs, mice, rats, and, recently, humans (12-14), are widely innervated by sensory nerve fibers (mainly A and C fibers). These fibers are responsible for the initial sensation of bone pain and the quality thereof (i.e., sharp pain vs. dull pain) (1,15).

Mouse bone tissue has a phenotypically more restricted set of primary afferent nerves than does mouse skin (16). Additionally, both preclinical and clinical studies have demonstrated that sympathetic and sensory nerve fibers innervating periosteum, cortical bone, and bone marrow are not merely static structures but can undergo active and pathological sprouting under acute and chronic painful pathological conditions. These studies also show that pharmacological blockade of this nerve sprouting in bone tissue results in analgesia (17-19). In the last 50 years, several clinical studies have shown that osteoplasty (injection of bone cement poly[methyl methacrylate]) into the target bone through a minimally invasive imaging-guided intervention, applied to patients with osteoporotic sacral fractures, multiple myeloma, and painful bone metastases in the spine and long bones (femur, humerus) can reduce pain and improve functioning and quality of life, as can opioid consumption (20-25). Using these lines of evidence, we proposed a summary of conceptual findings on osteogenic pain and major bone pain conditions.

I. Nerve Innervation and Skeleton Interoception

I.I. Nervous System Innervation

The periosteum and bone marrow, like other organs, have an abundance of sensory and autonomic nerve fibers, especially in areas where osteogenic activity is significant (2,26). According to recent anatomical investigations conducted on human cadaveric bone samples, the periosteum, cortical bone, and bone marrow are mostly innervated by A and C nerve fibers (12). An important function of sensory nerve fibers, particularly Aδ fibers and C fibers, is to convey information from bone tissue to the central neurological system (27).

Aδ fibers with thin myelination detect the majority of nonpainful mechanical or tactile sensations. Aδ fibers with high myelination detect painful mechanical stimuli. Unmyelinated C fibers transmit thermal, mechanical, chemical, and some unpleasant stimuli (29,28).

Up to 80% of the unmyelinated/thinly myelinated sensory nerve fibers that innervate the periosteum, mineralized bone, and bone marrow express TrkA and calcitonin gene–related peptides (CGRPs). This phenomenon may, in part, explain why therapies targeting the NGF/TrkA pathway are highly effective in attenuating skeletal pain (13,29) (Fig. 1).

Also, research has shown that sensory nerves may directly control bone cells by causing changes in osteoclast development and reduced bone density when the semaphorin 3A (Sema3A) gene is deleted from sensory neurons (30,31).

II. Bone Remodeling

Bone is a connective tissue that changes shapes continually due to the actions of osteoclasts, osteoblasts, and osteocytes. Bone remodeling consists of resorption, transition, and formation phases.

Osteoclasts originate from monocyte/macrophage precursor cells, and their differentiation is regulated by mesenchymal cells—including osteoblasts, chondrocytes, and osteocytes—that express the key osteoclast differentiation factor RANKL. Osteoblastic cells counteract RANKL activity by producing osteoprotegerin (OPG), a soluble decoy receptor that protects bone metabolism (30,33).

The transition phase is regulated by classical coupling factors such as insulin-like growth factor and transforming growth factor-β, which link bone resorption to subsequent bone formation. Sema3A, expressed by osteoblast lineage cells, acts as a potent osteoprotective factor by simultaneously inhibiting bone resorption and promoting bone formation. In this way, Sema3A coordinates osteoblast and osteoclast activity to favor bone mineral accrual. Importantly, Sema3A may play a crucial role during the bone formation phase by enhancing osteoblast-driven bone deposition while preventing osteoclast migration to these sites and thereby restraining the premature resorption of newly formed bone (31,32).

II.I. Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) give rise to osteoblasts, which aid in bone formation and repair tissue damage; in contrast, osteoclasts initiate the process of tissue breakdown (33,34). While undergoing differentiation into osteocytes implanted in the bone matrix, osteoblasts regulate bone remodeling by transmitting mechanical signals and detecting microfractures. Under normal conditions, this intricate system coordinates the actions of various cell populations, growth factors, and hormones to keep time and space in equilibrium (26).

II.II Sympathetic Activity

Increased sympathetic activity typically reduces bone mass by promoting osteoclast formation and inhibiting osteoblast function (35). Conversely, parasympathetic activity is believed to affect bone health positively. Both nicotinic and muscarinic acetylcholine receptors are present in osteoclasts and osteoblasts, with nicotinic receptor activation inducing osteoclast apoptosis (36). Mice that lack cholinergic receptors exhibit elevated osteoclast numbers and lifespans, leading to decreased bone mass (37). These neurons relay

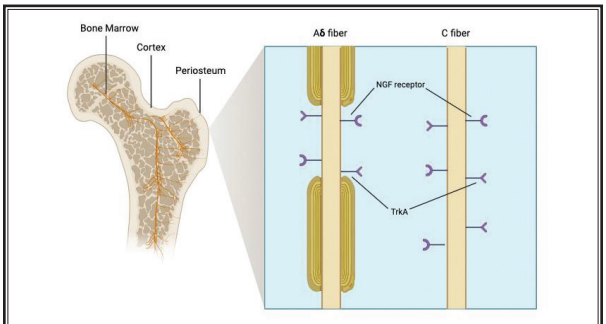


Fig. 1. *Unmyelinated Aδ and C fibers expressing TrkA and CGRP extend through the cortical bone and reach the marrow expressing TrkA and CGRP.*

stress signals such as exercise or temperature changes to sympathetic neurons in the spinal cord, which then activate postganglionic sympathetic neurons. This heightened sympathetic activity influences bone cell behavior by affecting the bone marrow and periosteum; however, the exact mechanism remains unclear (38). The β2-adrenergic receptor, present in both osteoblasts and osteoclasts, is considered the main mediator of sympathetic nerve action on bone remodeling, although the mode of interaction between nerves and bone cells is not fully understood (39).

II.III Osteoclast Activity

Mechanical stress activates bone responsiveness, a process that tries to repair damage and maintain skeletal integrity; this function is necessary because the skeleton is continually remodeling up to 20% of itself (40). Diseases marked by increased osteoclastic bone resorption often occur with pain, since osteoclasts are more commonly associated with skeletal pain and sensory innervation than osteoblasts and osteocytes are (41). Bisphosphonates and TRPV1 antagonists, which target osteoclast activity, are useful in mitigating bone pain. In OA pain models, osteoclasts produce the nerve-attractant factor NETRIN1. Pain-relieving effects are replicated when NETRIN1 is removed from osteoclasts, indicating that the NETRIN1 in osteoclasts is an important regulator of OA pain (44). Models of OA (42) show reduced pain and sensory nerve blockage when osteoclasts are inhibited by RANKL deletion in osteocytes or alendronate therapy (43).

A 2-way interaction seems to occur between sensory neurons and blood vessels in the regulation of skeletal pain; specifically, sensory nerves release neuropeptides such as CGRP and substance P, which encourage the formation of blood vessels (15).

However, nothing is known about how osteoblasts affect sensory innervation and skeletal pain directly. Influencing the afferent neural system via regulating osteoclast activity indirectly, osteoblasts may provide an unwelcoming environment for sensory innervation by repelling elements (26).

III. Etiologies and Concepts of Osteogenic Pain

Bone pain may be caused by common conditions such as trauma, inflammation, aging, and pathological conditions, including OA, autoimmune diseases, genetic mutations (e.g., autosomal recessive osteogenesis imperfecta), and cancer metastasis. If sensory nerve fibers are innervating bony tissue, the logical questions are how and by what these bony nociceptors are activated and/or sensitized to produce painful sensations in humans (nociception in rodents). Based on preclinical and clinical studies, we propose distinct but most likely overlapping events that underlie osteogenic pain.

First is a direct activation of mechanotransducers expressed by nociceptors innervating bone tissue under acute bone injury states (e.g., bone fractures and bone marrow aspiration) (47,48). Secondly, under nonmalignant (fracture, fibrous dysplasia) and malignant diseases (osteosarcoma, bone metastases by breast and prostate cancer cells), there is a marked influx of hematological and inflammatory cells into the bone tissue, which results in the activation and sensitization of bony nociceptors that express receptors for cytokines, chemokines, and inflammatory factors such as bradykinin, NGF, or prostaglandins that are frequently released upon tissue injury (17,49). Thirdly, a highly acidic environment is produced within the bone because of pathological osteoclast activation and enhanced bone resorption (e.g., bone metastases, postmenopause-related osteoporosis, fibrous dysplasia) (17,49). Thus, an increased release of protons and local acidosis leads to the activation and sensitization of several acid-sensing ion channels, including the transient receptor potential vanilloid 1 and acid-sensing ion channel 3, which are expressed in bone tissue (17,49). Fourthly, injury and damage to the distal processes of sensory nerve fibers that innervate the bone marrow under tumor growth have also been reported to occur (50). Fifthly, profound pathological sprouting and hyperinnervation of sensory neurons have also been observed in several preclinical models (fibrous dysplasia, breast cancer, prostate cancer, osteosarcoma, and multiple myeloma) as well as in bone samples from humans who have metastatic breast cancer and multiple myeloma (18,19,49). Previous studies have shown that ectopic sprouting of sensory nerve fibers results in hyperalgesia, allodynia, and spontaneous ectopic discharges that are perceived as highly painful in humans (16). Furthermore, in rodent models of bone cancer, blockade of this nerve sprouting with either anti-NGF or anti-netrin therapies results in analgesia (17,19). Altogether, the sprouting of nerve fibers within the affected bone may play a role in developing and maintaining osteogenic pain. Sixthly, previous studies demonstrate that the application of intraosseous pressure into the femoral bone marrow results in a barrage of the fir-

ing of spinal cord neurons and increases the expression of c-Fos (a marker of neuronal activity) in the ipsilateral superficial dorsal horn, causing referred pain and hyperalgesia in the corresponding skin areas, indicative of central sensitization (51,52). These findings suggest the CNS's pivotal role in transmitting osteogenic pain. Fig. 2 summarizes the main mechanisms of osteogenic pain (16,47-50).

IV. Major Bone Pain Conditions

IV.I. Bone Cancer Pain

One of the most prevalent sites for cancer to spread is to the bone (53).

Imaging studies may detect bone metastases even in the absence of symptoms, although cancer patients often describe bone pain, which can worsen with time

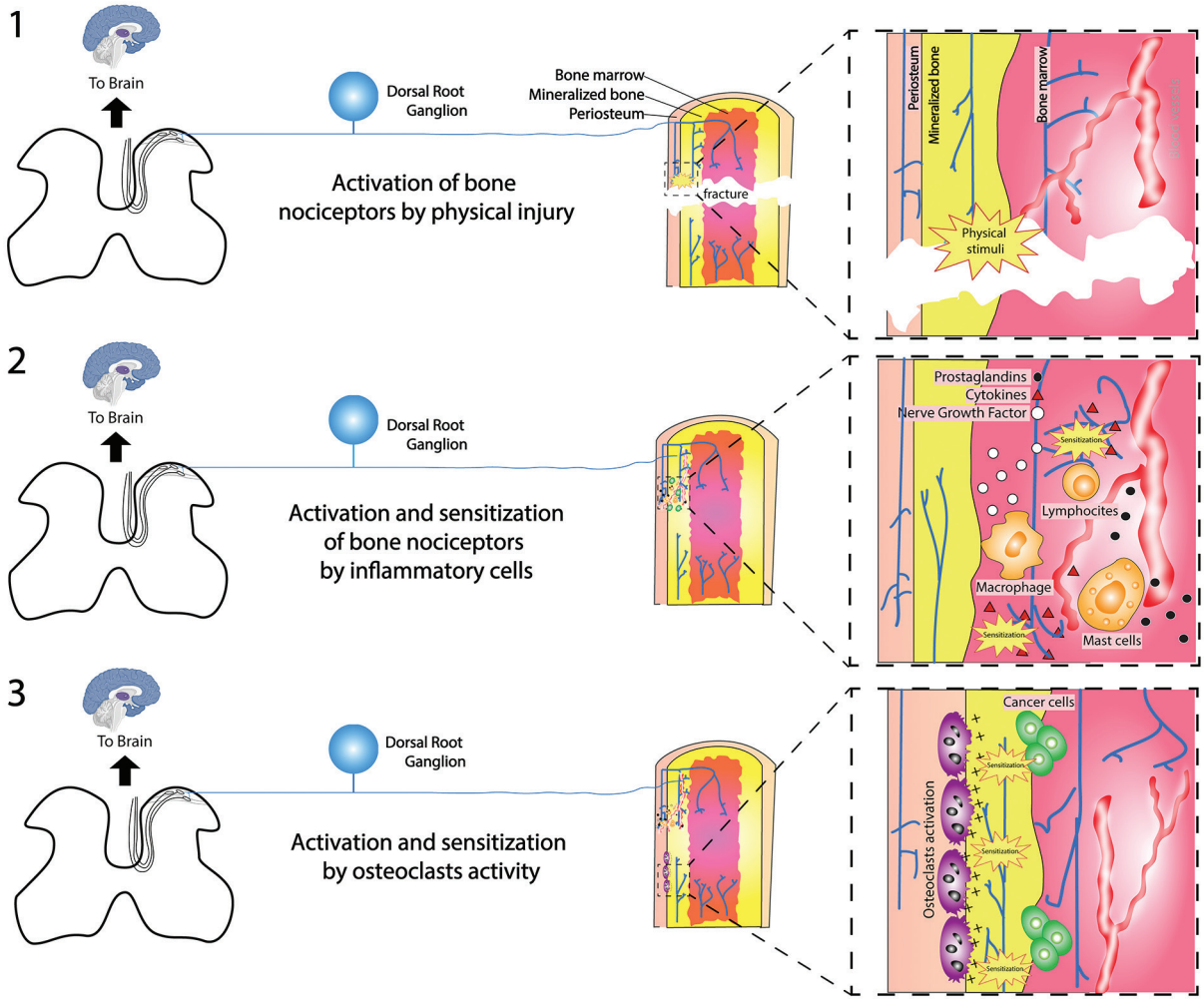


Fig. 2. *Potentially neurobiological mechanisms of osteogenic pain. The scheme illustrates the complex and overlying mechanisms that cause pain to originate from bone tissue. Osteogenic pain may originate from the direct activation of mechanosensitive nociceptors during acute injury, such as a fracture (1). Peripheral sensitization can be caused by increased synthesis and release of inflammatory mediators, such as cytokines, prostaglandins, and nerve growth factor [NGF] by immune and even tumor cells, which bind to their specific receptors on nerve endings and initiate osteogenic pain (2). Under certain pathologies (osteoporosis, fibrous dysplasia, or metastatic cancer), a pathological osteoclast activity creates an acidic (proton-rich) microenvironment that activates acid-sensing ion channels (e.g., TRPV1 and ASIC3), initiating the osteogenic pain (3).*

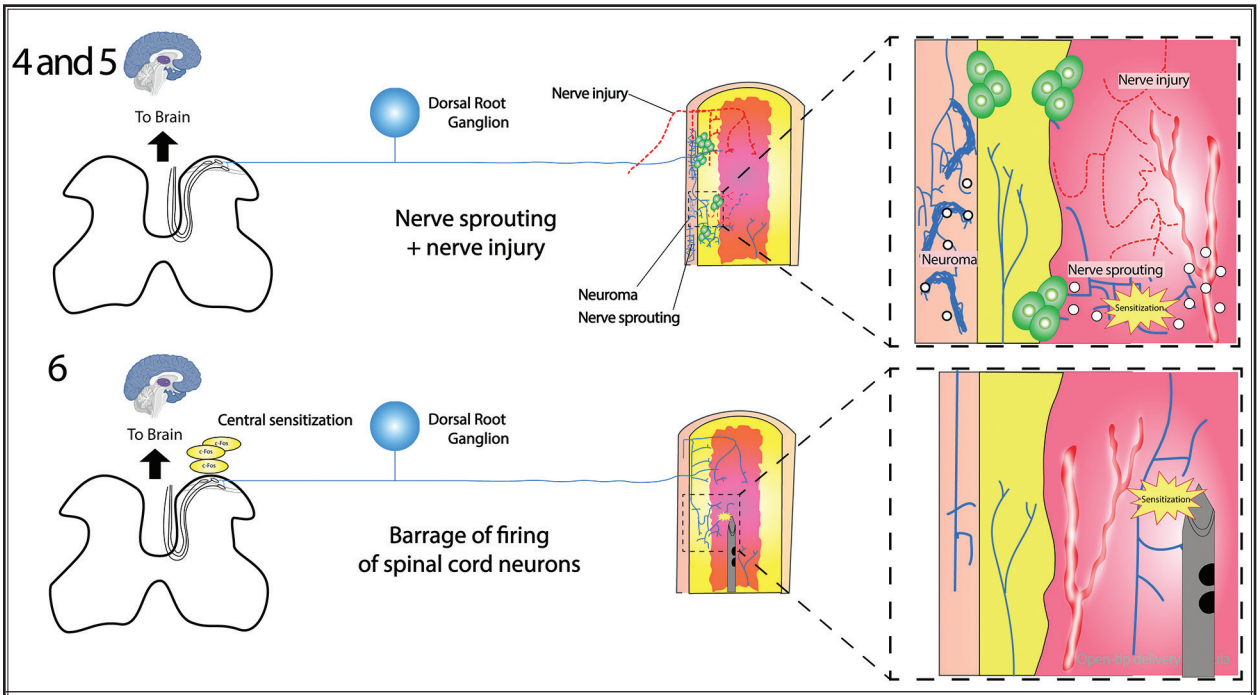


Fig. 2 cont. *Potentially neurobiological mechanisms of osteogenic pain. The scheme illustrates the complex and overlying mechanisms that cause pain to originate from bone tissue. In pathological chronic conditions such as bone cancer, pain is exacerbated by (4) direct nerve injury or damage and (5) abnormal sprouting of sensory nerve fibers, also known as hyperinnervation, resulting in hyperalgesia, allodynia, and spontaneous ectopic discharges. Finally, persistent and intense noxious signaling from the bone leads to central sensitization within the spinal cord dorsal horn, contributing to the maintenance of osteogenic pain and referred hyperalgesia (6).*

and be excruciatingly painful (2,3). Bone metastasis patients face the risk of fractures, hypercalcemia, and spinal cord compression, all of which may worsen patients' quality of life and require surgical intervention (2).

The concept of a premetastatic niche was first proposed by Kaplan et al (54). In addition, they reported the aforementioned information that many biochemical processes might lead to the formation of a premetastatic niche in bone (55,57). A few of these start in malignant primary tumors' systemic signals, whereas others are present in normal bone marrow. An increase in tumor cell seeding and the subsequent development of bone metastases from breast cancer is shown in animal studies due to interleukin IL-6 released by aged osteoblasts (58). This process leads to an increase in bone resorption mediated by osteoclasts. Osteoclast activity and bone resorption are both increased in the absence of estrogen and androgen. Consequently, the resorbed bone releases bone-specific factors, which foster an optimal environment for tumor cells to proliferate (56,57,59,60). According to Clézardin et al (59), early tumors may emit soluble chemicals that target stromal and/or bone cells, which might lead to metastatic colonization in the bone marrow. Paraneoplastic release of parathyroid hormone-related peptides (PTHrPs) or an aberrant activation of 25-OH vitamin D may exacerbate hypercalcemia in bone metastases, while enhanced osteoclastic bone resorption is the usual cause (61,62).

By blocking the action of IL-1β with either anakinra, an anti-IL-1 receptor antagonist, or canakinumab, an IL-1β-specific antibody, tumor cells in mice treated with those substances were able to avoid spreading into the bloodstream and from spontaneously forming metastases to human bone implants, unlike in the placebo group (58,63). To set up other tissues, such as bone, for metastatic colonization, primary tumors may release hypoxia-induced lysyl oxidase (LOX) into the circulation (59,60,64). Tsukasaki et al (65) and Clézardin et al (59) found that in animal models of breast and colon cancer, tumor-derived LOX and receptor activator of nuclear factor-kappaB (RANK) ligand (RANKL) synergistically accelerate osteoclastic bone resorption and progression of premetastatic osteolytic lesions in the bone.

Even before tumor cells reach this location, components inside exosomes released by cancer cells may seemingly affect the function of bone cells. Exosomes are tiny extracellular vesicles (30-120 nm) that contain DNA, RNA (mRNA, miRNA, and other noncoding RNAs), lipids, and proteins. Exosomes are produced by many cell types and then taken up by recipient cells (59,66).

In addition to molecular pathways seen in normal bone marrow, findings show that primary tumors may control the establishment of a premetastatic niche. This process is accomplished by secreting substances into the bloodstream that alter the process of bone remodeling (67).

IV.II. Bone and Joint Pain Due to OA

More than half of all instances of osteoarticular disorders consist of OA, and its incidence is on the rise globally, causing significant impairment and morbidity (68). Of all the symptoms of OA, pain is by far the most common (26). The pathogenesis of OA-related pain is complicated and includes neuropathic peripheral and central abnormalities as well as local inflammation, the last of which affects all joint tissues. The illness itself is a distinct entity (68).

Afferent sensory and sympathetic fibers both innervate the skeletal system (8). Research has shown that the primary sources of pain in OA joints are thin-myelinated or unmyelinated fibers that innervate the tissues around the joint (33,69). Table 1 describes the distribution and characteristics of these fibers.

As OA advances, subchondral bone remodeling becomes more pronounced (70). Zhu et al (69) uncovered the function of sensory innervation for OA pain in mice by studying osteoclast-initiated subchondral bone remodeling. Alendronate therapy lowered osteoclast activity, while RANKL knockout in osteocytes reduced osteoclast development, according to their results. Significantly, according to Zhu et al (69), those therapies reduced sensory nerve sprouting, abnormal subchondral bone remodeling, hyperexcitability of DRG neurons, and behavioral pain hypersensitivity in OA mice. Further, osteoclasts positive for tartrate-resistant acid phosphatase (TRAP) showed less OA pain behavior when Netrin-1 was knocked out (69). Consistent with these results, studies in the clinic demonstrated that MRI-observed subchondral bone marrow edema–like lesions (BMLs) are significantly associated with OA pain in patients (26,70).

According to the research findings of Serge et al, local inflammation plays a significant role in the pathogenesis of OA (71). C fibers exhibit 3 receptors in the joints: one for glial-derived neurotrophic factor (GDNF), one for ATP (P2X3), and one for nerve growth factor (TRKA) (72). Joint structures, with the exception of cartilage (73), include substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), and C-C motif chemokine ligands 2 (CCL2) as their mediators (72). Ryu et al and Zarebska et al found that CCL2 delayed the development of pain-like behavior and increased macrophage infiltration in the dorsal root ganglia, both of which contribute to pain sensitization in murine OA (74,75). NGF has been the focus of biological treatments due to its central involvement in joint pain and its importance as a component of C fibers (71).

The joints have also been shown to possess certain pain receptors that are involved in neuropathic pain: Descending inhibitory processes may target TRPV receptors, which are located in several joint structures (76). A study conducted by Kelly et al showed that injecting a TRPV1 antagonist into the joints of rats with an OA model reduced their pain behavior (77). Joint receptors such as the opioid (78) and cannabinoid (79) receptors, which are more numerous under inflammatory conditions, may also play a role in the pathophysiology of OA pain and be potential analgesic targets. A Serge et al study suggested that there may be a therapeutic opportunity to treat OA pain by targeting CB2 receptors. The results showed that systemic injection of a CB2-receptor agonist reduced OA-induced pain behavior and altered the alterations in circulating pro- and anti-inflammatory cytokines (71). CaV3.2, a T-type calcium

Table 1. *Distribution and characteristics of nociceptor fiber types in OA (33).*

Fiber Type	Myelination	Innervation Sites	Activated By
Aδ fibers	Myelinated	Synovial membrane, joint capsule, periarticular ligaments, menisci, adjacent periosteum, subchondral bone	Noxious mechanical, chemical, or thermal stimuli
C fibers	Unmyelinated	Synovial membrane, joint capsule, periarticular ligaments, menisci, adjacent periosteum, subchondral bone	Noxious mechanical, chemical, or thermal stimuli
Aβ fibers	Myelinated	Synovial membrane, joint capsule, periarticular bursae, fat pad, ligaments, menisci, adjacent bony periosteum	Joint movement (non-noxious stimuli)

channel, controls neuronal excitability and is involved in the processing of pain (80). Itson-Zoske et al showed recently that in a rat model of monosodium iodoacetate (MIA)–induced knee OA, there was an association between neuropathic pain behavior and elevated T-type/CaV3.2 activity in the primary sensory neurons (PSNs) of dorsal root ganglia (DRG) (81).

An increasing amount of data suggest the importance of central processes and sensitization in OA pain, as they have in other pain syndromes. Indeed, it is at the latter and chronic phases that the central processes may become most active (82). Analyses of functional magnetic resonance imaging (fMRI) and quantitative sensory testing (QST) have both detected central sensitization in OA (83). More research has shown central sensitization in female OA patients than in male OA patients, according to analyses of pain thresholds and sensitivity to various stimuli (84).

Interest in treating OA has always existed, since it is a chronic condition that impacts the quality of approximately 50 million individuals' lives in the US alone (85). However, no medicine has been authorized for the purpose of modifying the disease to alleviate its painful and debilitating effects (85). Traditional methods of treating OA pain, such as injecting hyaluronan or steroids into the joint, have had little success in alleviating both the pain itself and the symptoms experienced by patients (86). Much research has been conducted on the use of monoclonal antibodies (mAb) against IL-1, TNF, NGF, and VEFG as possible targeted therapies for OA, either as systemic or low-dose local treatments (26,85). Curiously, new prospective clinical trials have shown that umbilical cord particulate and human amniotic membrane have anti-inflammatory and anti-scarring properties. These substances may also have disease-modifying effects on OA joint pain, such as inhibiting pain, reducing inflammation, and preventing scarring (87). Therefore, according to Zhen et al, an effective and safe method for alleviating joint OA pain might be the intra-articular injection of amniotic membrane/umbilical cord particulate (26).

IV.III. Pain in Bone Autoimmune Diseases

An extremely prevalent kind of arthritis is rheumatoid arthritis (RA) (88). There are several potential causes of pain in RA, including inflammation in the periphery and abnormalities in processing information in the central nervous system (88). One mechanism of peripheral pain is the sensitization of nociceptors by joint inflammation; another is the direct activation of nociceptors (89). The responses of nociceptive neurons may be directly influenced by several inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), interleukin-6 (IL-6), and interleukin-17 (IL-17) (90, 91). The receptors for TNF-α, IL-1β, and IL-17 have been discovered by scientists on sensory neurons. The transmembrane signal-transducing component that binds to the IL-6 receptor complex was discovered in dorsal root ganglion neurons by Boettger (93) and Deng et al (92). Moreover, when normal rat knees are injected with IL-1β, TNF-α, IL-6, and IL-17A, the C fiber action potential frequency rises in both painless (less rotation) and painful (more rotation) knee rotations (89,94). Disruptions to the normal functioning of the pain-regulating systems in the central nervous system (CNS) are the root cause of central pain (95). In a process like that of peripheral sensitization, hyperalgesia and allodynia can be caused by dysregulation of the central nervous system pain pathways, such as inactivation or overactivation (96). A discordance between the circuits that initiate pain and those that terminate it might be the root cause of pain-related disorders (97,98). Central sensitization, descending inhibitory pathways, and ascending facilitatory pathways are the 3 primary methods by which the central nervous system controls pain (89,98-100). The brain stem, spinal cord, and brain all communicate via these routes. The rostral ventromedial medulla (RVM) and periaqueductal gray (PAG) are important regulatory areas (91,99,101). Multiple brain areas, including those responsible for processing emotions and stress, communicate with the PAG, which in turn affects how pain is perceived (101). After that, the PAG sends signals to the RVM and brain stem and then releases serotonin. Depending on the pathways that are active, the RVM may either prevent or enhance pain, with different proteins and peptides playing important roles (95,96,101). Greater pain sensitivity and broader receptive fields are hallmarks of central sensitization, which develops in the spinal cord's dorsal horn. Various processes, including the activation of NMDA receptors and the production of pain-regulating peptides, initiate the acute and chronic stages, respectively (100). Much study has been conducted on the causes of central nervous system pain in fibromyalgia and OA, but the amount of study concerning the causes of the same condition in rheumatoid arthritis (RA) is far greater. New research conducted by Jansen suggests that inflammation is not the only factor that might cause RA discomfort to persist. Noninflamma-

tory variables also play a big role (102). It is critical to have a thorough grasp of these noninflammatory variables to improve therapy techniques (91). Since many of the symptoms that patients experience might be related to other conditions, getting a proper diagnosis quickly is essential for optimal illness treatment. To establish a correct diagnosis, it is necessary to properly apply and understand ACR-EULAR criteria, identify and quantify diagnostic biomarkers, and associate the acquired data with imaging modalities. For RA, the end objective of therapy is a decrease in symptoms or complete remission with the use of strong pharmacological interventions (88).

IV.IV. Low Back Pain and Bone Pain

Everyone, regardless of age or gender, may experience musculoskeletal pain (MSKP), which can take many forms. In recent years, MSKPs have become more common (103). A major source of impairment across all age groups, low back pain (LBP) accounts for 570 million prevalent cases globally and is the leading cause of musculoskeletal disorders overall (104).

Although the precise cause of CLBP has not been identified, several anatomical structures have been proposed as possible sources of pain, including nerve roots, soft tissue, vertebrae, zygapophyseal and sacroiliac joints, and intervertebral discs (105). Disc degeneration, facet joint arthritis, spinal stenosis, and radicular compression are the other pathological changes that compose the remaining instances of CLB (105).

Degeneration of the facet joints and intervertebral discs, as well as ectopic discharges of DRG neurons, leads to prevalent causes of back pain, including inflammation, neural foramen, constriction of the spinal canal, lateral recess dorsal root compression, and radicular pain. Mechanical shock is the most prevalent cause of this pain (105,106). When cells in the nucleus pulposus are subjected to physiological mechanical stress, it improves the signaling of parathyroid hormone (PTH) and facilitates its transport to the cilia (106,107). PTH can stimulate the transcription of integrin $\alpha v\beta 6$, which in turn activates TGF-β. To keep the intervertebral discs in a stable state, the signaling cascade involving TGF-β, connective tissue growth factor (CCN2), and matrix proteins is triggered (26,107,108).

There are currently no long-term solutions to LBP; all therapies are symptomatic and do nothing to address the underlying degeneration and etiology of the condition. Intradiscal injections of amniotic membrane and umbilical cord particles also alleviated pain without causing side effects in individuals with discogenic LBP, in a result similar to the suppression of OA pain after intra-articular medication injections (109,110).

Limitations

Most mechanistic data supporting osteogenic pain are derived from preclinical models, and several limitations should be considered when interpreting and translating these findings to clinical practice.

Across studies, variability in species/strain, gender, age, skeletal site, disease induction methods, and outcome measures can contribute to heterogeneous results. In addition, many models emphasize evoked reflex behaviors, which may not fully capture spontaneous pain or functional impairment. More clinically relevant models, standardized reporting (e.g., randomization/blinding where feasible), and parallel human biomarker/imaging studies will be important for strengthening the translational evidence base.

Conclusions

Future priorities include improving the clinical relevance of experimental models, expanding human validation (including imaging and biomarker studies), and developing practical tools to assess osteogenic pain and its impact on quality of life across oncologic and nononcologic conditions. Together, these efforts may accelerate translation of skeletal pain mechanisms into more precise diagnostics and personalized treatment pathways.

We propose the term "osteogenic pain" as a mechanistically informed concept to describe pain that originates from, or is maintained by, pathological processes in bone tissue and its microenvironment. Adopting this framework may help guide phenotyping, target selection, and the development of safer nonopioid strategies that preferentially modulate peripheral pain generators (e.g., NGF/TrkA signaling, osteoclast activity, and acid-sensing pathways) while complementing established analgesic approaches. In many nonmalignant skeletal pain conditions, NSAIDs remain a cornerstone of multimodal management, highlighting the importance of developing adjunctive, mechanism-based options that may improve the efficacy and tolerability of treatments.

This review synthesizes recent rodent and human evidence indicating that bone tissue is a direct generator of pain and that bone pain reflects integrated signaling among sensory afferents, immune cells, and bone-remodeling cells within the skeletal microenvironment.

Mechanisms such as inflammatory mediator release, osteoclast-driven acidosis, NGF/TrkA-dependent sensitization and sprouting, and central sensitization appear to contribute—often in overlapping ways—across malignant and nonmalignant skeletal diseases.

Author Contributions

RP: original idea, conception; MS: literature research, writing; SD: editing, critical revision; JMJA: literature research, writing; BCHP: literature research, writing; AAE: editing, revision, final approval.

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