Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Chronic Pain and Bone-Related Pathologies: A Narrative Review

Marie-Eva Pickering[1], Marine Delay[2,3], Véronique Morel[2]

[1]Rheumatology Department, CHU Gabriel Montpied, Clermont-Ferrand, 63000, France; [2]PIC/CIC Inserm 1405, CHU Gabriel Montpied, Clermont-Ferrand, France; [3]Neurodol Inserm 1107, Faculté de Médecine, Université Clermont-Auvergne, Clermont-Ferrand, France

Correspondence: Marie-Eva Pickering, Rheumatology Department, CHU Gabriel Montpied, Clermont-Ferrand, 63000, France, Email mepickering@chu-clermontferrand.fr

Purpose: Pain related to bone may occur as a result of trauma, bone fracture, genetic disease, arthritis, benign or malignant primary bone tumors and bone cancer metastases. We discuss the pathophysiology of chronic bone-related pain, treatment options and therapeutic perspectives.

Methods: Using predefined terms, we searched PubMed, MEDLINE, and Google Scholar for meta-analyses, evidence-based reviews, and clinical practice guidelines. This narrative article reviews pathologies linked to chronic bone pain and discusses the preventive and therapeutic strategies for better bone pain management.

Results: Pathophysiology of bone-related pain is complex, especially in cancer conditions and missing gaps are underlined. Treatment of pain, after adequate evaluation, includes classical analgesics, adjuvants for neuropathic and refractory pain, specific bone drugs, surgery and non-pharmacological approaches. Prevention of chronic bone pain encompasses prevention of central sensitization and of causal diseases.

Conclusion: Translational research, drug repurposing, an interdisciplinary approach and a person-centered assessment to evaluate, beyond pain, physical, social and functional abilities, are proposed future directions to improve chronic bone pain management and optimize independence and quality of life.

Summary: Chronic bone-related pain is frequent and is associated with an impairment of quality of life. In this review, we summarize the pathophysiology of chronic bone pain, describe treatment approaches and envisage new avenues for pain alleviation. Our article will help doctors manage chronic bone pain and address unmet needs for future research to alleviate bone-related pain.

Keywords: bone, prevention, treatment, pain

Introduction

Musculoskeletal conditions affect 1.71 billion people worldwide according to an analysis of Global Burden of Disease 2019 data[1] and are the highest contributor to disability and to the global need for rehabilitation.[2] Low back pain, that results from different injuries and conditions, including bone diseases, is the main contributor to the overall burden of musculoskeletal conditions (570 million prevalent cases worldwide). Bone-related pathologies may affect all ages but their prevalence increases with aging. They often coexist with other noncommunicable diseases and increase the risk of developing other comorbidities: ie osteoporosis is associated with cardiovascular disease and arterial calcifications,[3] osteoarthritis with sarcopenia,[4] both with disability, impaired quality of life, morbidity and mortality.

Bone-related pain may occur as a result of trauma, injury and disease, with bone fracture, osteoarthritis, rheumatoid arthritis, spondyloarthritis, benign or malignant primary bone tumors or bone cancer metastases.[5] Rare and genetic bone and joint diseases, affecting young people and children (ie osteogenesis imperfecta, fibrous dysplasia) are also associated with bone pain. Chronic bone pain, defined as pain lasting for more than 3 months,[6] has an increased prevalence with age (osteoarthritis, low back pain, osteoporotic fracture) since aging is associated with reduced bone mass and muscle, tendon and bone quality. It may be excruciating and refractory to treatment; it is responsible for impaired quality of life, mobility and independence, increased morbidity and burden of disease. Considering the high prevalence of bone-related pain and

Received: 16 March 2024
Accepted: 21 August 2024
Published: 5 September 2024

the heterogeneity of its aetiology, this review reports the pathologies linked to chronic bone-related pain and discusses the preventive and therapeutic strategies for better pain management.

Methods

We searched PubMed, Google Scholar, and Cochrane databases and the reference lists of relevant citations for publications on bone pain with combinations or isolated keywords such as bone pain, prevention, treatment, with no limit in language or publication date. Search terms included chronic pain, bone, cancer, osteoporosis, rheumatoid arthritis (RA) spondyloarthritis (SA), genetic bone diseases. We included reviews, clinical practice and relevant articles in the articles written in the English language. We excluded articles if no full-text document was available for review.

Pathologies Causing Chronic Bone Pain

Chronic bone-related pain may develop at any age from benign or malignant pathologies (Table 1). At evaluation, bone-related pain may be difficult to differentiate from pain arising from surrounding structures, muscles, tendons or ligaments, and depends on the pathology phenotype.[7]

One of the commonest pathologies, osteoarthritis, affects millions of people worldwide, especially after 65 years old. It is characterized by focal areas of articular cartilage loss in synovial joints, associated with varying degrees of osteophyte formation, subchondral bone change and synovitis. The classification criteria for osteoarthritis are described by the Osteoarthritis Research Society International (OARSI) and other Societies.[8] Joint damage is caused by a mix of local, systemic and mechanical factors, and various minor genetic abnormalities have been described. It is well recognized today that osteoarthritis pain is only weakly linked to the clinical context, and poorly correlated with joint lesions visualized by standard radiography.[9] With joint damage, nociceptors located in the subchondral bone and the synovium may be responsible for pain stimuli activated during normal activities of daily living such as walking. A chronic, sterile, low-grade inflammation state[10] driven by endogenous signals in the absence of infection, "inflamma-ging", is also described in osteoarthritis as part of the aging process. Animal models of induced and spontaneous pain have been used to study the characteristics of pain in osteoarthritis.[11] However, differences in the model used to induce osteoarthritis, length of follow-up (often limited to 2–4 weeks), diversity of the tests used still make it difficult to obtain a consensus on long-term behavior after joint damage, but allows a mapping of pain behavior in relation to the molecular, tissue and level changes at the dorsal horn of the spinal cord.[9]

One of the main manifestations of inflammatory rheumatic diseases, like rheumatoid arthritis, axial spondyloarthritis (AxSpA) and psoriatic arthritis (PsA), is pain. RA is a chronic, immune-mediated, systemic inflammatory disease of the synovial joints that affects 1.5% of the population and presents with swelling, stiffness and tenderness in more than one joint. Pain arises from chronic inflammation and progressive deterioration of the joint, and combines pain central and peripheral sensitization features.[12] It is reported that up to 90.4% of RA patients visit a health professional for severe pain,[13] but a small proportion will have refractory RA despite optimal management.[14] Chronic inflammatory low back

Table 1 Pathological Causes and Physiopathology of Chronic Bone-Related Pain

Pathological Causes	Pathophysiology	
Osteoarthritis	Focal areas of cartilage loss in synovial joints. Osteophyte formation, subchondral bone change, synovitis, inflammation.	Pain Peripheral and Central Sensitization
Rheumatoid arthritis Spondyloarthritis Psoriatic arthritis	Chronic autoimmune inflammatory disease. Cartilage and bone damage.	
Osteoporotic Fracture	Diminished bone mass density (postmenopause, corticotherapy, post-bariatric surgery). Osteoclast hyperactivity and bone fragility	
Bone cancer	Metastases or primary. Osteolytic lesions, Diminished bone mass density	

pain[15] is a common feature of AxSpA that affects 1% of the population.[16] Back pain is associated with morning stiffness, improvement with exercise but not with rest. Psoriatic arthritis affects approximately 6% to 48% of patients with psoriasis.[17] The highest priorities for patients with inflammatory rheumatic disease are pain relief and function improvement. Osteomyelitis, characterized by progressive inflammatory bone destruction, with antibiotics as first-line treatment is also accompanied by severe pain and disability.[13]

Chronification of pain associated with the occurrence of a bone fracture is another common issue. Changes in lifestyle in the general population practicing more sports activities both among young people and older people who have a longer life expectancy, make sports activities the third cause of fractures in the general population, after falls in the elderly and direct trauma or injury. In older people, the literature reports that 40–50% of women and 13–22% of men will experience an osteoporotic fracture during their lifetime. Osteoporotic fractures represent a major health problem, entailing heavy medical, social and health expenditure.[18] There is currently a lack of effective treatment options to relieve acute fracture pain without potentially interfering with bone healing. As in general surgery, adequate pain treatment in the acute phase will determine the occurrence of chronic pain. Inadequate pain control immediately after and up to 3 months after a fracture is the strongest predictor of chronic pain at 7 years.[19] When the fracture heals, pain decreases with the formation of a bone callus and bone repair. A severe fracture and/or one that does not heal appropriately, for example in bone metabolic disorders such as osteoporosis, can lead to chronic pain. Chronic pain is known to have a very negative impact on quality of life, and psychosocial factors are important determinants of pain severity.[20]

Benign bone tumors (osteochondroma, giant cell tumor, osteoid osteoma, chondroblastoma) are non-cancerous masses characterized by significant osteoclastic activity which weakens the bone, increases the risk of fracture and is associated with local pain. Among rare diseases, fibrous dysplasia of the bones (prevalence of 1/30,000), common in adults (81%) and children (49%) in both lower limbs, head and spine,[21] is responsible for bone deformities, fractures, nerve compression and bone pain. Pain is often one of the first symptoms of the disease and does not dissipate with age. Paget's disease (prevalence of 0.3%) is an unusual bone growth disorder, characterized by excessive osteoclastic activity with increased osteoblastic activity, leading to the formation of disorganized bone, less compact, more fragile, highly vascularized and inducing a risk of fracture.[22] Often asymptomatic, 25% of patients report deep and severe nocturnal bone pain.

Chronic pain may also be due to primary malignant bone tumors, <0.5% of malignant tumors (multiple myeloma, osteosarcoma, adamantinoma, Ewing's sarcoma, chondrosarcoma, chordoma, fibrosarcoma, etc), but in adults, bone metastases are much more frequent than primary malignant bone tumors. It is estimated that 60–84% of patients with advanced cancer experience varying degrees of bone pain with persistent bone pain usually getting worse over time and at night. Prostate, lung, breast and colorectal are the most frequent cancers[23] and breast, lung, prostate and kidney carcinomas the most frequent sources of bone metastases. Osteolytic metastases (75%) are more frequent than osteo-condensing metastases (15%) with the consequent risk of fracture and pain chronification.

Evaluation of Bone Pain

In randomised trials and in real-life studies, pain is assessed by clinical examination, patient-reported outcomes and with a large number of validated tools. As it is difficult to objectively measure pain in rheumatology, behavioral testing methods have been developed (for example in rheumatoid arthritis with significant positive correlations between total pain behavior scores and measures of disease activity:[24] behavioural testing may be included as an objective outcome measure in clinical trials with RA patients. Somatosensory testing looking for allodynia, hyperalgesia, and sensations like tingling, burning, stabbing etc, are landmarks of neuropathic pain.[25] Assessment of nociplastic pain, that presents with altered nociception despite no clear evidence of nociceptive or neuropathic pain, relies on clinical examination. Neuropathic and nociplastic pain sometimes coexist and patients may have residual symptoms even after pharmacological treatment (for example in spondyloarthritis with biological disease-modifying antirheumatic drugs).[26]

There is no specific tool to measure bone pain and auto evaluation of pain is the gold-standard: eleven-point scales are often used, including Visual Analogue Scale (VAS) (0 to 10), Verbal Rating Scale (VRS) (0 no pain – 10 (or 100) worst possible) or Facial Scale Score (FSS, 0–10)). Neuropathic Pain may be assessed with several questionnaires (Leeds Assessment of Neuropathic Symptoms and Signs pain scale (LANSS),[27] Neuropathic Pain in 4 questions (DN4),[28] Pain

Detect[29]). The Brief pain Inventory (BPI) assesses the severity of pain and its impact on functioning.[30] In non-communicating patients, observational scales are used to detect the presence of pain.

Quality of life (QOL) questionnaires include also one or several pain items, as in Short-Form Health Survey (SF-8, SF-36). Specific questionnaires have been validated in osteoporosis: the Japanese Osteoporosis Quality Of Life (JOQOL) questionnaire, consisting of 38 questions in six categories (pain, daily living activity, recreational and social activities, general health conditions, posture and figure, falls and the psychological effects), the mini-Osteoporosis quality of life (OQLQ), derived from the 30-item Osteoporosis quality of life questionnaire, that includes two questions in each of five domains, two questions (pain or standing pain) related to pain and analyzed individually, the European Foundation for Osteoporosis (QUALEFFO-41) consisting in 41 questions in 5 domains: pain, physical function, social function, general health perception, and mental function. Other questionnaires may be added – for example in osteoarthritis – Western Ontario and McMaster Universities Arthritis Index (WOMAC), SF-36 scales with the addition of the Short-Form McGill Pain Questionnaire (MPQ-SF), to provide a more complete pain characterization. The 24-item Roland Morris Disability Questionnaire (RDQ) ranging from 0 "no disabilities" to 24 "maximal disability" allows measurement of physical functioning [references in[31]].

Pathophysiology of Chronic Bone Pain

Chronic bone pain is complex and may have concomitant inflammatory and neuropathic characteristics. Bone is innervated[5,31] by sensory fibers at different levels of the bone structure: periosteum, mineralized bone and bone marrow with a respectively decreasing fiber density. A fracture or a tumor damages the fibrous mesh of the bone architecture and disturbs the normal pH, leading to local acidosis, that is reinforced by the overactivity of osteoclasts. Mechanosensitive A-delta and C fibers express ion channels, including acid-sensing ion channels (ASIC1,3) and transient receptor potential vanilloid channels (TRPV1) known to induce pain (see references in[31]). Pain is not always related to the severity of bone loss, as reflected by the non-correlation between bone mineral density and pain report, and it has been shown that there are different subtypes of osteoclasts that may modulate pain. Osteoclasts communicate with other cells, immune, stromal and inflammatory cells for the production of neuropeptides (ie nerve growth factor (NGF), substance P…), with sympathetic nerves and may release algogenic products. Osteocytes, that are very abundant in bone, are also implicated, as osteocyte-related cytokines like tumor necrosis factor (TNFα) regulate osteoclast formation by enhancing receptor activator nuclear factor kB ligand (RANKL) and sclerostin, and inflammatory cytokines have osteoclastogenic effects. After the acute episode, chronic bone pain may develop with peripheral and central pain sensitization. Phosphorylation and activation of mitogen-activated protein kinases (MAPKs) and gene transcription factors, upregulation of neurotransmitters, glial cells, activation of N-methyl-D-aspartate receptors (NMDARs) with modulation of descending pain pathways may lead to central pain sensitization (see references in[31]). The neuropathic character of chronic bone pain should not be underestimated; it may be associated with nociceptive pain, for example in vertebral osteoporotic fractures, where neuropathic pain is present after 20% of fractures.[32]

In chronic inflammatory disease, the synovium and capsule of the joint are rich in primary Aα and Aβ sensory neurons for mechanosensation and Aδ and C fibers for nociception. Synovitis can directly activate and sensitize the afferent nerve[33] and synovial fluid concentrations of neuromessengers (bradykinin, prostaglandins) and cytokines (tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17), calcitonin gene-related peptide (CGRP), and nerve growth factor-β (NGF-β)) are significantly increased in RA. Nociceptive pain is also due to tissue inflammation in psoriatic and spondyloarthritis. Additional pain mechanisms, neuropathic and nociplastic, may also be present and must be looked for, as additional treatment may complement immunotherapy.[26,34]

In cancer bone pain[35–37] with primary malignant tumors or with metastases, the mechanisms of pain development are similar to non-cancer conditions, but largely emphasized, with proton production by the osteoclasts and also by the invading cells. The rich hematopoietic network of the bone provides cancer cells with ideal conditions to grow. In the majority of cancers, the tumor mass consists of tumor and tumor stromal cells, including macrophages, neutrophils, T-lymphocytes, fibroblasts, and endothelial cells. These cells secrete factors already mentioned (prostaglandins, bradykinin, TNFα, endothelins, interleukins-1 and −6, epidermal growth factor, transforming growth factor-alpha, platelet-derived growth factor, and NGF), which directly sensitize or excite primary afferent fibers. Osteolytic and osteoblastic cancers are all characterized by proliferation and hypertrophy of osteoclasts.[38] Recent work[39] has suggested that these sensory fibers could also contribute to the progression of cancer in the bone and to its dissemination. Tumor

microenvironment and neoplastic and nervous cells cross-talk are indeed thought important both for cancer bone pain and, probably, for cancer progression.[40,41] Intractable pain reduces both the quality of life and survival in cancer, and in tumor-bearing mice, it has been shown that cancer aggravation may be due to persistent pain signals with an increased expression of pain-related mediators in sensory neurons[41].

There may be variations in the prevalence and management of chronic bone pain across different regions and populations but these aspects are poorly reported in the literature and would need to be studied specifically.

Animal and translational research widens knowledge on the complex bone pathophysiology, on sensory fibers, subpopulations of dorsal root ganglion neurons, bone innervation, transcription profiles, peripheral and central pain sensitization mechanisms.[42,43] One of the main gaps in translational research is that bone pain in patients may be of different types, with diverse characteristics, and be linked to several and mixed etiologies.[43]

Prevention of Chronic Bone Pain

For most bone diseases, prevention of chronic pain necessitates the prevention or treatment of the pathology itself, as pain is often a comorbidity, but the effective causal treatment leading to a remission of the disease is not always possible. Prevention of the development of chronic pain after a fracture or after surgery follows general recommendations to minimize the risk of pain sensitization. Catastrophizing, mental health, preoperative knee pain, and pain at other sites are the strongest independent predictors of persistent pain after knee arthroplasty.[44,45] Predictors of residual low back pain and chronic pain after acute osteoporotic compression fracture are proposed, and the severity of pain before or in early post-surgery is one of the commonest predictors,[46,47] suggesting that early and effective, pain relief strategy is important to avoid pain sensitization. Predictors of chronic pain for all osteogenesis imperfecta types are age, use of a wheelchair, and the number of fractures/year.[48] Blood markers have also been proposed to clinically predict relevant knee osteoarthritis progression defined as the combination of both joint structure and pain worsening over 48 months.[49] Prevention of the development of chronic degenerative diseases includes also dietary approaches, like the Mediterranean diet,[50] calcium intake,[51] exercise[52] or treating other comorbidities like diabetes[53] in osteoporosis. In osteoarthritis, activities can focus on preventing risk factors or preventing progression to disease or illness once risk factors have been identified. Some risk factors are present early in life and these efforts can bridge the entire lifespan.[54] Concerning cancer, with between a third and a half of cancers being preventable on the basis of present knowledge of risk factors, primary prevention must be prioritized.[55]

Therapeutic Strategies for Chronic Bone Pain

Management of chronic pain follows recommendations to combine drug and non-drug approaches (Table 2) in order to improve the synergy of action, especially since chronic pain is often associated with psychosocial impairment.

Table 2 Therapeutic Strategies

Pathological Causes	Therapeutic Strategies			
	Pharmacological			Additional Approaches
	Analgesics	Co-analgesics	Disease specific drugs	
Osteoarthritis	Paracetamol, NSAIDs, opioids	Glucocorticoïdes (when inflammation) Antidepressants, antiepileptics, topical lidocaine and capsaicin (when neuropathic pain). Ketamine, Methadone (when refractory pain)	Variable indirect effect on pain relief	Surgery Non pharmacological Interdisciplinary
Rheumatoid arthritis, Spondyloarthritis, Psoriatic arthritis				
Osteoporotic Fracture				
Bone cancer (primary or metastases)				

Drug Treatment

Drug treatment includes conventional analgesic drugs, co-analgesics, disease-modifying agents, with more specific treatment for cancer-related pain and generally dose adaptation according to age, comorbidities and other drugs.

Analgesics and Coanalgesics

The usual recommendations on nociceptive pain with paracetamol, non-steroidal anti-inflammatories (NSAIDs) for pain of mild to moderate intensity, then opioids in the event of moderate to severe pain, apply for the management of non-cancer and cancer pain. The improved tolerance of selective cyclooxygenase 2 (COX-2) inhibitors compared with traditional NSAIDs has not been demonstrated. NSAIDs are more effective than paracetamol for inflammatory pain and are recommended in osteoarthritis when paracetamol and local NSAIDs are ineffective; topical route should be considered before oral route for osteoarthritis of the knee and hand, but all NSAIDs have known gastric and renal side effects that limit their use to the lowest dosage for the shortest time. Prescription of opioids (tramadol, codeine, morphine, oxycodone, buprenorphine, hydromorphone…) is related to the intensity of pain and not to the severity of the disease, and they are used for chronic cancer and non-cancer bone pain. Opioid switching is a therapeutic strategy to replace one strong opioid with another, the aim being to improve the benefit/risk ratio, especially in palliative care. By changing the molecule, pharmaceutical formulation or route of administration, it is indicated in selected situations for insufficient pain control, and when adverse effects are not easily controlled by symptomatic treatments. Recommended analgesic dosages, starting doses and routes of administration must be adapted to age and clinical condition of the patient. Side-effects of opioids are well known and their incidence may be limited by applying expert recommendations and best practice guidelines.[56]

For neuropathic pain, antidepressants such as tricyclic antidepressants and noradrenaline/serotonin reuptake inhibitors, gabapentinoid antiepileptics, topical anesthetics (lidocaine 5%, capsaicin 8% plasters) and other molecules are recommended according to the clinical context, all the more since chronic pain is often accompanied by depression. Other adjuvants include corticosteroids, radiopharmaceuticals, NMDAR antagonists, local anesthetics and a2-adrenergic agonists. A drug with a dual mode of action like tramadol, which has a centrally opioidergic mode of action and an inhibitory effect on serotonin/norepinephrine reuptake, is also used in bone pain as nociceptive and neuropathic bone pain often coexist. Ketamine or methadone are also used in specific conditions, in particular in pain resistant to any other treatment and in palliative care.[7] In pain related to cancer and cancer treatments, in addition to these drugs, corticosteroids and hormone therapy are useful for analgesia. Attacks of paroxysmal pain may require the use of sublingual fentanyl in oncology. Despite pain guidelines, treatment discontinuation is frequent, and some patients still suffer from uncontrolled pain due to lack of efficacy, analgesic tolerance, drug side effects or drug interactions. There are still many barriers to adequate pain relief for both the patient and the health care practitioner.

Disease-Modifying Agents

In addition to analgesics, a number of drugs have been shown to participate to pain relief, but in not all the studies. Bisphosphonates (BPs), structural analogues of inorganic pyrophosphate, are the most commonly drug used in osteoporosis for the prevention and treatment of postmenopausal osteoporosis and are effective in preserving bone mineral density, especially in patients with high risk of fracture. Several prospective observational and randomized trials show a concomitant improvement in pain with all BPs.[31]

In several studies on osteoarthritis, BPs have also shown to improve pain scores, with pamidronate, zoledronate and risedronate.[57,58] Likewise, pamidronate and zoledronate have shown a significant diminution of pain in complex regional pain syndrome (CRPS)[59] compared with placebo or reference therapy. In inflammatory rheumatological diseases, BPs were shown to diminish pain in spondyloarthritis[60] but do not have any significant direct effect on disease activity or pain in rheumatoid arthritis.[61] Several non-controlled trials also underlined BPs could diminish pain associated with hip and knee aseptic osteonecrosis.[62]

In bone metastases, a Cochrane meta-analysis shows the positive effect of BPs to alleviate pain in breast cancer,[63] and in multiple myeloma, the European Society of Medical Oncology (ESMO) recommends the use of pamidronate, zoledronate or denosumab for at least 2 years.[64]

Denosumab, a human IgG2 antibody, binds with high affinity and inhibits RANKL, a major regulator of osteoclast formation and activation. Denosumab has been followed in 5 prospective or retrospective studies, on a total of 750 patients, with an improvement in pain and low back pain.[31] In contrast, denosumab has a rebound effect upon discontinuation that can lead to multiple vertebral fractures. Rare adverse events such as osteonecrosis of the jaw and atypical femoral fracture have been described.

Calcitonin, a hormone secreted by the thyroid gland, regulates the metabolism of phosphorus and calcium in the body. It inhibits bone resorption by direct action on osteoclasts and has shown analgesic activity in animal models as well as in clinical trials in humans. Calcitonin is also useful in pain associated with compression fractures,[65] and is an interesting therapeutic option in Paget's disease.[66]

Teriparatide and Abaloparatide, two parathyroid hormone (PTH) analogues are anabolic agents that affect the PTH1 receptor and are treatments for osteoporosis. They increase bone formation, but stimulation of osteoclasts by osteoblasts leads to a rebound in bone resorption. All clinical studies[31] with teriparatide, observational, including the European Forsteo study, and randomized, versus placebo or versus different types of BPs, show an improvement in back pain related to fracture osteoporosis, but with more side effects than calcium or vitamin D.

Janus-kinase inhibitor (baricitinib) achieved in rheumatoid arthritis significantly greater improvements in patient-reported pain than patients treated with a tumor necrosis factor (TNF) blocker (adalimumab), despite both treatments being associated with similar changes in standard clinical measures and markers of inflammation.[67]

Other Strategies

Other avenues of analgesic treatment are promising. For example, inhibitors of Cathepsin K, the proteolytic enzyme produced by osteoclasts, have been shown in animal models to exhibit modest chondroprotective and pain-reducing effects.[57] Sclerostin, produced by osteocytes, prevents bone formation by inhibiting Wnt signaling in the cells: antisclerostin antibodies have been shown in animals to augment the size and the strength of the intervertebral disc by stimulating Wnt signaling, an interesting approach since intervertebral disc degeneration is a leading cause of low back pain.[68] Likewise, the sequestration of NGF or the inhibition of TrkA channels[69] offer new mechanistic possibilities, but can only be approved in humans if the profile of adverse effects is satisfactory. Plants used in traditional Chinese medicine have also been evaluated: for example, aconitine alleviates both cold and mechanical allodynia in cancer-induced bone pain via the regulation of TRPA1 receptor.[69]

Surgery and interventional radiology also increasingly have their place in the management of pain, particularly in cancer.[7,56] Surgery, alone or combined with radiation therapy, radiofrequency ablation or cryotherapy are often the first step in pain management, especially in palliative care. Percutaneous cryotherapy is considered as a safe and effective technique in the treatment of benign and malignant musculoskeletal tumors, a first option and a valid alternative to radiofrequency ablation. For painful bone metastases, it is advised when other standard treatments (radiotherapy, bisphosphonate therapy, and chemotherapy) are no longer effective in controlling the disease or when they cannot be repeated.[70] With the increased incidence of vertebral osteoporotic fractures, kyphoplasty and vertebroplasty techniques are treatments that may provide pain relief and functional recovery, although often associated with several side effects. A recent meta analysis[71] showed kyphoplasty to be superior to vertebroplasty in terms of reducing cement leakage and of increasing postoperative vertebral body height; but this is more costly and has a longer operative time.

Non-Pharmacological Pain Management

Non-pharmacological pain management interventions are strongly recommended in synergy with pharmacological approaches especially for persistent pain. Nurses, physiotherapists and psychologists have a role to play in the management of bone pain and in clinical decision-making. According to the type and etiology of bone pain, massage, heat/cold, exercise are advised. WHO launched the Rehabilitation 2030 initiative in 2017[2] to draw attention to the profound unmet needs for rehabilitation worldwide, and to highlight the importance of strengthening rehabilitation in health systems. It is also developing a package of interventions for rehabilitation including low back pain, osteoarthritis, rheumatoid arthritis, sarcopenia, fractures in the extremities with a list of essential interventions for rehabilitation and the resources required to deliver them safely and effectively. These interventions will be relevant for people at all stages of life, along the

continuum of care, across all service delivery platforms, and across all world regions, with a specific focus on low -and middle-resource contexts.[2] Currently, a multidisciplinary approach is recommended in musculoskeletal/bone pain and even more frequently in cancer bone pain.

Conclusion and Future Directions

Chronic bone pain significantly impairs the quality of life. Over the past ten years, progress has been made in understanding the complex pathophysiology of non-cancer and cancer bone pain, in clinical and in animal models of bone pain. Care must be multimodal, systemic and local. A thorough analysis of the type of pain and its evaluation are necessary to prescribe adequate treatment. In addition to conventional analgesics, a number of drugs such as bisphosphonates, denosumab or teriparatide have also shown analgesic properties. The development and combination of interventional and pharmacological techniques aim to provide synergy for the treatment of bone-related pain in order to maintain quality of life and functional status of patients who often have psychological comorbidities.

Translational research must be pursued to fill the knowledge gap on bone pain pathophysiology, on the development of chronic pain in different bone pain conditions, on local joint destruction and systemic bone loss, and on the mechanistic of pain sensitization. These are challenges as several bone pathologies often coexist in patients, and chronic pain is frequently accompanied in real-life by anxiety, depression, stress and polypharmacy. Another drawback of translation is that the safety threshold of once promising drugs in preclinical situations is not always attained resulting in non-registration.

More research is also needed on bone marrow stem cells/bone marrow stromal cells which have been shown to produce powerful analgesic effects in animal models of inflammatory pain, neuropathic pain, and cancer pain.

Drug repurposing is another emerging direction of research: for example, saracatinib originally developed in oncology but then deprioritized, is currently being investigated in bone pain through national programs.[72] More research is needed but resources are necessary to facilitate it.

Bone cancer pain remains a real issue: prevention or at least limitation of central pain sensitization with systemic antihyperalgesic drugs to suppress the activity of sensory fibers at bone level could offer new opportunities in the treatment of cancer progression and cancer-related bone pain. A link between pain sensitization and cancer progression has been recently suggested and this needs to be explored.[39]

In the clinical context, person-centered assessment for evaluating physical, social and functional abilities may help to address issues of barriers to patient participation. It is indeed pivotal to stress the importance of an interdisciplinary approach to manage chronic bone pain, involving healthcare providers, physiotherapists, pain specialists, and mental health professionals in order to provide a more holistic approach.

Finally, dietary/nutrition, exercise/mobility, adequate analgesia approaches must be considered in the prevention of underlying pathologies and generators of chronic bone pain, in order to maintain mobility, dexterity, participation in social activities, independence and quality of life.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors received no funding for this manuscript.

Disclosure

Marie-Eva Pickering, Marine Delay and Véronique Morel declare no conflicts of interest related to this manuscript.

References

1. Cieza A, Causey K, Kamenov K, et al. Global estimates of the need for rehabilitation based on the global burden of disease study 2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2021;396(10267):2006–2017. doi:10.1016/S0140-6736(20)32340-0
2. Available from: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions. Accessed September 02, 2024
3. Pickering ME. Cross-talks between the cardiovascular disease-sarcopenia-osteoporosis triad and magnesium in humans. *Int J Mol Sci*. 2021;22(16):9102. PMID: 34445808. doi:10.3390/ijms22169102
4. Pickering ME, Chapurlat R. Where two common conditions of aging meet: osteoarthritis and sarcopenia. *Calcif Tissue Int*. 2020;107(3):203–211. PMID: 32424600. doi:10.1007/s00223-020-00703-5
5. Mantyh PW. Mechanisms that drive bone pain across the lifespan. *Br J Clin Pharmacol*. 2019;85(6):1103–1113. PMID: 30357885. doi:10.1111/bcp.13801
6. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain*. 2015;156(6):1003–1007. PMID: 25844555. doi:10.1097/j.pain.0000000000000160
7. Frost CØ, Hansen RR, Heegaard AM. Bone pain: current and future treatments. *Curr Opin Pharmacol*. 2016;28:31–37. PMID: 26940053. doi:10.1016/j.coph.2016.02.007
8. Luyten FP, Bierma-Zeinstra S, Dell'Accio F, et al. Toward classification criteria for early osteoarthritis of the knee. *Semin Arthritis Rheum*. 2018;47(4):457–463. doi:10.1016/j.semarthrit.2017.08.006
9. Vincent TL. Peripheral pain mechanisms in osteoarthritis. *Pain*. 2020;161(Suppl 1):S138–S146. PMID: 33090747. doi:10.1097/j.pain.0000000000001923
10. Motta F, Barone E, Sica A, Selmi C. Inflammaging and Osteoarthritis. *Clin Rev Allergy Immunol*. 2023;64(2):222–238. PMID: 35716253. doi:10.1007/s12016-022-08941-1
11. Miller RE, Malfait AM. Osteoarthritis pain: what are we learning from animal models? *Best Pract Res Clin Rheumatol*. 2017;31(5):676–687. doi:10.1016/j.berh.2018.03.003
12. Iyer P, Lee YC. Why it hurts: the mechanisms of pain in rheumatoid arthritis. *Rheum Dis Clin North Am*. 2021;47(2):229–244. PMID: 33781492. doi:10.1016/j.rdc.2020.12.008
13. Sánchez-Flórez JC, Seija-Butnaru D, Valero EG, Acosta CDPA, Amaya S. Pain management strategies in rheumatoid arthritis: a narrative review. *J Pain Palliat Care Pharmacother*. 2021;35(4):291–299. PMID: 34623946. doi:10.1080/15360288.2021.1973647
14. Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis*. 2018;77(7):966–969. PMID: 29588276. doi:10.1136/annrheumdis-2017-212862
15. Magrey MN, Mease PJ. Pain in axial spondyloarthritis: more to it than just inflammation. *J Rheumatol*. 2021;48(11):1632–1634. PMID: 33934079. doi:10.3899/jrheum.210137
16. Sieper J, Poddubnyy D. Axial spondy loarthritis. *Lancet*. 2017;390(10089):73–84. PMID: 28110981. doi:10.1016/S0140-6736(16)31591-4
17. Kobayashi H, Fujita R, Hiratsuka S, et al. Differential effects of anti-RANKL monoclonal antibody and zoledronic acid on necrotic bone in a murine model of Staphylococcus aureus-induced osteomyelitis. *Orthop Res*. 2022;40(3):614–623. PMID: 33990977. doi:10.1002/jor.25102
18. Alves CJ, Neto E, Sousa DM, et al. Fracture pain-Traveling unknown pathways. *Bone*. 2016;85:107–114. PMID: 26851411. doi:10.1016/j.bone.2016.01.026
19. McVeigh LG, Perugini AJ, Fehrenbacher JC, et al. Assessment, quantification, and management of fracture pain: from animals to the clinic. *Curr Osteoporos Rep*. 2020;18(5):460–470. PMID: 32827293. doi:10.1007/s11914-020-00617-z
20. Cox N, Hawarden A, Bajpai R, et al. The relationship between pain and depression and anxiety in patients with inflammatory arthritis: a systematic review protocol. *Rheumatol Int*. 2024;44(3):435–440. PMID: 37700079. doi:10.1007/s00296-023-05450-y
21. Chapurlat RD, Gensburger D, Jimenez-Andrade JM, et al. Pathophysiology and medical treatment of pain in fibrous dysplasia of bone. *Orphanet J Rare Dis*. 2012;;7(Suppl 1):S3. 10.1186/1750-1172-7-S1-S3
22. Bouchette P, Boktor SW. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2023.
23. Zajączkowska R, Kocot-Kępska M, Leppert W, et al. Bone pain in cancer patients: mechanisms and current treatment. *Int J Mol Sci*. 2019;20(23):6047. 10.3390/ijms20236047
24. Anderson KO, Bradley LA, McDaniel LK, et al. The assessment of pain in rheumatoid arthritis. validity of a behavioral observation method. *Arthritis Rheum*. 1987;30(1):36–43. doi:10.1002/art.1780300105
25. Scholz J, Finnerup NB, Attal N. Attal N et al.The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. 2019;160(1):53–59. PMID: 30586071. doi:10.1097/j.pain.0000000000001365
26. Al Mohamad F, Rodriguez VR, Haibel H, et al. Association of nociplastic and neuropathic pain components with the presence of residual symptoms in patients with axial spondyloarthritis receiving biological disease-modifying antirheumatic drugs. *RMD Open*. 2024;10(1):e004009. doi:10.1136/rmdopen-2023-004009
27. Bennett M. The LANSS pain scale: the Leeds assessment of neuropathic symptoms and signs. *Pain*. 2001;92(1–2):147–157. PMID: 11323136. doi:10.1016/s0304-3959(00)00482-6
28. Van Seventer R, Vos C, Meerding W, et al. Eur J Linguistic validation of the DN4 for use in international studies. *Pain*. 2010;14(1):58–63. PMID: 19282208. doi:10.1016/j.ejpain.2009.01.005
29. Freynhagen R, Baron R, Gockel U, et al. pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22(10):1911–1920. PMID: 17022849. doi:10.1185/030079906X132488
30. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap*. 1994;23(2):129–138. PMID: 8080219.
31. Pickering ME, Javier RM, Malochet S, et al. Osteoporosis Treatment and Pain relief: a scoping review. *European J Pain*. 2024;28(1):3–20
32. Moretti A, Liguori S, Paoletta M, et al. Characterization of neuropathic component of back pain in patients with osteoporotic vertebral fractures. *NeuroRehabilitation*. 2022;51(2):325–331. PMID: 35599506. doi:10.3233/NRE-220040
33. Cao Y, Fan D. Y pain mechanism in rheumatoid arthritis: from cytokines to central sensitization. *Mediators Inflamm*. 2020;12:2076328. doi:10.1155/2020/2076328
34. Mease PJ. Navigating the complexity of pain in psoriatic arthritis and axial spondyloarthritis. *Curr Opin Rheumatol*. 2024;36(4):282–288. PMID: 38690783. doi:10.1097/BOR.0000000000001023

35. Haroun R, Wood JN, Sikandar S. Mechanisms of cancer pain. *Front Pain Res*. 2023;3:1030899. PMID: 36688083. doi:10.3389/fpain.2022.1030899
36. Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain*. 1997;69(1):1–18. doi:10.1016/S0304-3959(96)03267-8
37. Zheng XQ, Wu YH, Huang JF, et al. Neurophysiological mechanisms of cancer-induced bone pain. *J Adv Res*. 2021;35:117–127. PMID: 35003797. doi:10.1016/j.jare.2021.06.006
38. Jimenez-Andrade JM, Mantyh WG, Bloom AP, et al. Bone cancer pain. *Ann N Y Acad Sci*. 2010;1198(1):173–181. PMID: 20536932. doi:10.1111/j.1749-6632.2009.05429.x
39. Yoneda T, Hiasa M, Okui T, et al. Cancer-nerve interplay in cancer progression and cancer-induced bone pain. *J Bone Miner Metab*. 2023;41(3):415–427. 10.1007/s00774-023-01401-6
40. Cippitelli M, Stabile H, Kosta A, et al. Role of NF-κB signaling in the interplay between multiple myeloma and mesenchymal stromal cells. *Int J Mol Sci*. 2023;24(3):1823. 10.3390/ijms24031823
41. Tanaka K, Kondo T, Narita M, et al. Cancer aggravation due to persistent pain signals with the increased expression of pain-related mediators in sensory neurons of tumor-bearing mice. *Mol Brain*. 2023;16(1):19. 10.1186/s13041-023-01001-5
42. Jurczak A, Delay L, Barbier J, et al. Antibody-induced pain-like behavior and bone erosion: links to subclinical inflammation, osteoclast activity, and acid-sensing ion channel 3-dependent sensitization. *Pain*. 2022;163(8):1542–1559. 10.1097/j.pain.0000000000002543
43. Zhen G, Fu Y, Zhang C, et al. Mechanisms of bone pain: progress in research from bench to bedside. *Bone Res*. 2022;10(1):44. 10.1038/s41413-022-00217-w
44. Lewis GN, Rice DA, McNair PJ, et al. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth*. 2015;114(4):551–561. PMID: 25542191. doi:10.1093/bja/aeu441
45. Zeeni C, Abou Daher L, Shebbo FM, et al. Predictors of postoperative pain, opioid consumption, and functionality after arthroscopic shoulder surgery: a prospective observational study. *J Orthop Surg*. 2022;30(1):10225536221094259. PMID: 35393908. doi:10.1177/10225536221094259
46. Firanescu CE, Venmans A, de Vries J, et al. predictive factors for sustained pain after (sub)acute osteoporotic vertebral fractures. combined results from the VERTOS II and VERTOS IV trial. *Cardiovasc Intervent Radiol*. 2022;45(9):1314–1321. PMID: 35680675. doi:10.1007/s00270-022-03170-7
47. Inose H, Kato T, Ichimura S, et al. Predictors of residual low back pain after acute osteoporotic compression fracture. *J Orthop Sci*. 2021;26(3):453–458. PMID: 32593545. doi:10.1016/j.jos.2020.04.015
48. Rodriguez Celin M, Kruger KM, Caudill A, et al. A multicenter study to evaluate pain characteristics in osteogenesis imperfecta. *Am J Med Genet A*. 2023;191(1):160–172. PMID: 36271817. doi:10.1002/ajmg.a.63009
49. Zhou K, Li YJ, Soderblom EJ, et al. A "best-in-class" systemic biomarker predictor of clinically relevant knee osteoarthritis structural and pain progression. *Sci Adv*. 2023;9(4):eabq5095. 10.1126/sciadv.abq5095
50. Quattrini S, Pampaloni B, Gronchi G, et al. The Mediterranean diet in osteoporosis prevention: an insight in a peri- and post-menopausal population. *Nutrients*. 2021;13(2):531. 10.3390/nu13020531
51. Cano A, Chedraui P, Goulis DG, et al. Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide. *Maturitas*. 2018;107:7–12. PMID: 29169584. doi:10.1016/j.maturitas.2017.10.004
52. Zitzmann AL, Shojaa M, Kast S, et al. The effect of different training frequency on bone mineral density in older adults. A comparative systematic review and meta-analysis. *Bone*. 2022;154:116230. PMID: 34624560. doi:10.1016/j.bone.2021.116230
53. Zawada A, Ratajczak AE, Rychter AM, et al. Treatment of diabetes and osteoporosis-a reciprocal risk? *Biomedicines*. 2022;10(9):2191. 10.3390/biomedicines10092191
54. Whittaker JL, Runhaar J, Bierma-Zeinstra S, et al. A lifespan approach to osteoarthritis prevention. *Osteoarthritis Cartilage*. 2021;29(12):1638–1653. PMID: 34560260. doi:10.1016/j.joca.2021.06.015
55. Vineis P, Wild CP. Global cancer patterns: causes and prevention. *Lancet*. 2014;383(9916):549–557. PMID: 24351322. doi:10.1016/S0140-6736(13)62224-2
56. Available from: https://www.iasp-pain.org/. Accessed September 02, 2024
57. Cai G, Aitken D, Laslett LL, et al. Effect of intravenous zoledronic acid on tibiofemoral cartilage volume among patients with knee osteoarthritis with bone marrow lesions: a randomized clinical trial. *JAMA*. 2020;323(15):1456–1466. doi:10.1001/jama.2020.2938
58. Seefried L, Genest F, Baumann J, et al. Efficacy of zoledronic acid in the treatment of nonmalignant painful bone marrow lesions: a triple-blind, randomized, placebo-controlled phase III clinical trial (ZoMARS). *J Bone Miner Res*. 2022;37(3):420–427. doi:10.1002/jbmr.4493
59. Fassio A, Mantovani A, Gatti D, et al. Pharmacological treatment in adult patients with CRPS-I: a systematic review and meta-analysis of randomized controlled trials. *Rheumatology*. 2022;61(9):3534–3546. 10.1093/rheumatology/keac060
60. Wang CR, Tsai YS, Whang-Peng J. Zoledronic acid monotherapy improves osteoarticular involvement in SAPHO syndrome. *Scand J Rheumatol*. 2020;49(5):419–421. doi:10.1080/03009742.2020.1769179
61. Le Goff B, Heymann D. Pharmacodynamics of bisphosphonates in arthritis. *Expert Rev Clin Pharmacol*. 2011;4(5):633–641. PMID: 22220307. doi:10.1586/ecp.11.40
62. Pijnenburg L, Felten R, Javier RM. A review of avascular necrosis, of the Hip and beyond. *Rev Med Interne*. 2020;41(1):27–36. doi:10.1016/j.revmed.2019.10.332
63. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO clinical practice guidelines. *Ann Oncol*. 2020;31(12):1650–1663. doi:10.1016/j.annonc.2020.07.019
64. Mhaskar R, Kumar A, Miladinovic B, et al. Bisphosphonates in multiple myeloma: an updated network meta-analysis. *Cochrane Database Syst Rev*. 2017;12(12):CD003188. doi:10.1002/14651858.CD003188.pub4
65. Boucher E, Rosgen B, Lang E. Efficacy of calcitonin for treating acute pain associated with osteoporotic vertebral compression fracture: an updated systematic review. *CJEM*. 2020;22(3):359–367. doi:10.1017/cem.2019.490
66. Merlotti D, Rendina D, Cavati G, et al. Drug treatment strategies for paget's disease: relieving pain and preventing progression. *Expert Opin Pharmacother*. 2023;28:1–13. PMID: 36961938. doi:10.1080/14656566.2023.2196011
67. Simon LS, Taylor PC, Choy EH, et al. The Jak/STAT pathway: a focus on pain in rheumatoid arthritis. *Semin Arthritis Rheum*. 2021;51(1):278–284. PMID: 33412435. doi:10.1016/j.semarthrit.2020.10.008
68. Kroon T, Bhadouria N, Niziolek P, et al. Suppression of sost/sclerostin and dickkopf-1 augment intervertebral disc structure in mice. *J Bone Miner Res*. 2022;37(6):1156–1169. PMID: 35278242. doi:10.1002/jbmr.4546

69. Jin X, Cheng J, Zhang Q, et al. Aconitine - A promising candidate for treating cold and mechanical allodynia in cancer induced bone pain. *Biomed Pharmacother*. 2023;161:114284. PMID: 36868017. doi:10.1016/j.biopha.2023.114284
70. Scandiffio R, Bozzi E, Ezeldin M, et al. Curr med imaging. *Imag-Guid Cryother Musculoskel Tumors*. 2021;17(2):166–178. PMID: 32842945. doi:10.2174/1573405616666200825162712
71. Daher M, Kreichati G, Kharrat K, et al. Vertebroplasty versus kyphoplasty in the treatment of osteoporotic vertebral compression fractures: a meta-analysis. *World Neurosurg*. 2023;171:65–71. PMID: 36455843. doi:10.1016/j.wneu.2022.11.123
72. Krishnamurthy N, Grimshaw AA, Axson SA, et al. Drug repurposing: a systematic review on root causes, barriers and facilitators. *BMC Health Serv Res*. 2022;22(1):970. PMID: 35906687. doi:10.1186/s12913-022-08272-z