■ REVIEW ARTICLE ■ SPINE SURGERY AND RELATED RESEARCH

Pathomechanisms and management of osteoporotic pain with no traumatic evidence

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Abstract:

Introduction: Osteoporosis is a pathological state with an unbalanced bone metabolism mainly caused by accelerated osteoporotic osteoclast activity due to a postmenopausal estrogen deficiency, and it causes some kinds of pain, which can be divided into two types: traumatic pain due to a fragility fracture from impaired rigidity, and pain derived from an osteoporotic pathology without evidence of fracture. We aimed to review the concepts of osteoporosis-related pain and its management.

Methods: We reviewed clinical and basic articles on osteoporosis-related pain, especially with a focus on the mechanism of pain derived from an osteoporotic pathology (i.e., osteoporotic pain) and its pharmacological treatment.

Results: Osteoporosis-related pain tends to be robust and acute if it is due to fracture or collapse, whereas pathology-related osteoporotic pain is vague and dull. Non-traumatic osteoporotic pain can originate from an undetectable microfracture or structural change such as muscle fatigue in kyphotic patients. Furthermore, basic studies have shown that the osteoporotic state itself is related to pain or hyperalgesia with increased pain-related neuropeptide expression or acid-sensing channels in the local tissue and nervous system. Traditional treatment for osteoporotic pain potentially prevents possible fracture-induced pain by increasing bone mineral density and affecting related mediators such as osteoclasts and osteoblasts. The most common agent for osteoporotic pain management is a bisphosphonate. Other non-osteoporotic analgesic agents such as celecoxib have also been reported to have a suppressive effect on osteoporotic pain.

Conclusions: Osteoporotic pain has traumatic and non-traumatic factors. Anti-osteoporotic treatments are effective for osteoporotic pain, as they improve bone structure and the condition of the pain-related sensory nervous system. Physicians should always consider these matters when choosing a treatment strategy that would best benefit patients with osteoporotic pain.

Keywords:

osteoporotic pain, osteoporosis, anti-osteoporotic treatment

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Introduction

Chronic pain derived from musculoskeletal disorders plays a key role in the health profile of the general elderly population[1]. and it leads to impairments in quality of life (QOL) and in activities of daily living (ADLs), resulting in dependency, institutionalization, and increased health care costs[2]. In particular, lower back pain (LBP) is one of the most important public health issues, as it is one of the most common symptoms that middle-aged and older people experience in their lives[3].

Among postmenopausal women, a significant increase in patients with LBP is often observed[4], and it is mainly due to osteoporosis, which is a pathological state with unbalanced bone metabolism chiefly caused by accelerated osteoporotic osteoclast activity due to a postmenopausal estrogen deficiency. Osteoporosis can cause pain from two main pathologies. First, pain can be due to a bone fracture, especially in the vertebrae and femoral neck because of their decreased bone rigidity (e.g., a fragility fracture). Its incidence according to the skeletal site is reported to be 27% of vertebral fracture, 19% of wrist, 14% of hip, 7% of pelvic, and

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33% of other sites[5]. Vertebral fragility fractures are especially associated with significant rates of morbidity and mortality. This results in excess medical expenditures of ≥ $1 billion in the US[6]. Second, pain can originate from the osteoporotic state itself without any evidence of a fracture. A recent population-based survey of 3,097 older subjects (≥65 years old) reported that older adults with musculoskeletal complaints, including osteoporosis and chronic back pain, have considerable ADL problems[7] due to pain.

Regarding the spinal osteoporosis itself, several kinds of osteoporotic agents are available: antiresorptive agents such as antibisphosphonates/denosumab, bone anabolic agents such as teriparatide, and other agents such as calcitonin, a selective estrogen receptor modulator (SERM), and Vitamin D. A previous systematic review shows the high evidence of preventing vertebral fractures in bisphosphonates, denosumab, and teriparatide with a relative risk reduction from 0.40 to 0.60[8]. However, the pathomechanisms and treatment for osteoporosis-related pain have not been adequately addressed yet.

The current article reviews osteoporosis-related pain, especially with a focus on LBP due to non-traumatic pain.

1) Traumatic osteoporosis-related pain with fracture or collapse

Osteoporotic patients tend to have fractures due to impaired bone mineral density (BMD). The main types of osteoporotic fractures are a (1) clinical fracture with a vertebral fracture or collapse with a distinguishing pain, including non-bony union or pseudoarthrosis, and a (2) morphometric fracture with gradual progression and little or almost no pain. Clinically, an osteoporosis-related fragility fracture is the main cause of LBP in elderly, with a 6%-8% incidence in women in their 60s and a ≥30% incidence in those in their late 70s, and half of the individuals tend to have multiple vertebral fractures[9]. Some studies have reported that the 5-year survival rate is significantly lower in those with a fragility fracture of the vertebrae and femoral neck than in those with other fractures, which suggests the importance of treating these fractures to improve patients' ADL and QOL as well as control their pain[10]. Some of these fragile vertebral fractures result in a non-bony union (pseudoarthrosis) with more than a 9-month history[5], which causes chronic back pain in the elderly. Though the actual incidence of the vertebral pseudoarthrosis is not clear, its incidence is estimated to amount to approximately 10% of the whole incidence of vertebral fragility fractures[11] followed by possible impairment in ADL and QOL. Toyone et al. has reported that the changes in vertebral wedging between standing and supine position are significantly associated with back pain[12]. For those with pseudoarthrosis, analgesic agents such as NSAIDs and acetaminophen are administered[13,14]. Some osteoporotic agents are reported to alleviate pain as is described later. Orthotic braces in the acute phase are reported to be effective in some systematic reviews, while its evidence level is relatively low[13-16]. When the pain is refractory to these kinds of conservative treatments, surgical treatments are available such as anterior decompression and stabilization[17], osteotomy/shortening[18], and percutaneous methods such as vertebroplasty and kyphoplasty[19-23]. These surgeries are also important for preventing delayed neurologic deficit after vertebral arthrosis[11,24,25]. However, a morphometric fracture is commonly observed in osteoporotic patients in their 60s and 70s with a progressive decrease in their height by about 1 cm yearly due to gradual progressive vertebral collapse[26]. A previous study showed that pain from this kind of slowly progressing acute fracture can be diagnosed using magnetic resonance imaging, single photon emission computed tomography radioisotope, and bone scintigraphy in addition to radiographs[27].

2) Osteoporotic pain derived from an osteoporotic pathology

In contrast to patients with pain from a fragility fracture, some osteoporotic patients complain of vague LBP with discomfort without any evidence of a clinical fracture[28]. The pain can be derived from multiple factors, including undetectable traumatic factors such as microfractures. Furthermore, in osteoporotic patients without any evidence of fractures, pain originates from an altered construction of bone and/or osteoporotic pathology. In patients with a degenerative hunched back, chronic LBP can be derived from deformed elements such as facet joints, cartilage, and ligament tissues surrounding the intervertebral discs as well as from muscle tissues and fascia that support the spine. Particularly, when the deformity of the lumbar spine is kyphotic, the erector spinae muscles become stretched, causing constant muscle contraction to cope with the condition, resulting in chronic muscle fatigue. These conditions induce increased intramuscular pressure with tense fascia, which result in an ischemic status in the muscle with chronic dull pain. Thus, these changes in the muscle cause LBP even for a short period (e.g., while standing and walking)[29-36]. The relationship between spinal kyphosis and the structural and functional parameters of trunk muscles should be investigated[36]. A previous basic study suggested that the involvement of inflammation of the fascia in the back could alter the gait pattern in rodents[37].

In addition, the osteoporotic state itself is related to pain[38,39]. Some basic studies have shown that the pathology itself induces specific hypersensitivity to pain, which is an unusual symptom of menopause[40,41]. This kind of osteoporotic pain tends to have a chronic course, whereas traumatic osteoporotic pain tends to develop into acute pain. Herein, pain derived from osteoporosis without any fractures or injuries is defined as osteoporotic pain (Fig. 1).

The Mechanism of Osteoporotic Pain

Basic studies have shown evidence of osteoporotic pain using an osteoporotic animal model of ovariectomized (OVX) rats, which exhibit similar hormonal changes to that

of osteoporotic patients. Regarding pain, these osteoporotic models reportedly show hyperalgesia with significantly shortened latencies of tail withdrawal from hot water[42] and long-term, formalin-induced licking[43]. The altered pain threshold in OVX rats can be caused by two anatomical factors: changes in the local tissue and changes in the nervous system.

The vertebral body itself is anatomically innervated by pain-related intravertebral sensory nerve fibers (Fig. 2)[39,44], and nociceptors respond to mechanical, thermal, and chemical stimuli. Injury or inflammation results in the release of various chemical mediators (e.g., prostaglandins, cytokines, and growth factors). These chemical mediators stimulate osteoclast activity, activate nociceptors, and decrease their threshold for activation[45,46]. Additionally, transient-receptor potential vanilloid 1 (TRPV1) has also been reported to be upregulated in the dorsal root ganglion (DRG) of OVX rats[39]. TRPV1 is a ligand-gated, non-selective cation channel preferentially expressed in pain-related, small-diameter primary afferent neurons[47,48], and it responds to capsaicin and noxious heat and acid. Osteoporotic osteoclasts degrade bone minerals by secreting protons through the vacuolar H^+-ATPase, creating local acidic microenvironments by inflammation[49,50], which should evoke the stimulation of TRPV1. Furthermore, this acidic microenvironment produced by inflammation stimulates acid-sensing ion channels (ASICs) in acid-sensing nociceptors[51,52]. These stimulations evoked by osteoporotic osteoclasts lead to the chronic increased expression of inflammatory pain-related neuropeptides, calcitonin gene-related peptides (CGRP), and DRG neurons, innervating osteoporotic vertebrae[39].

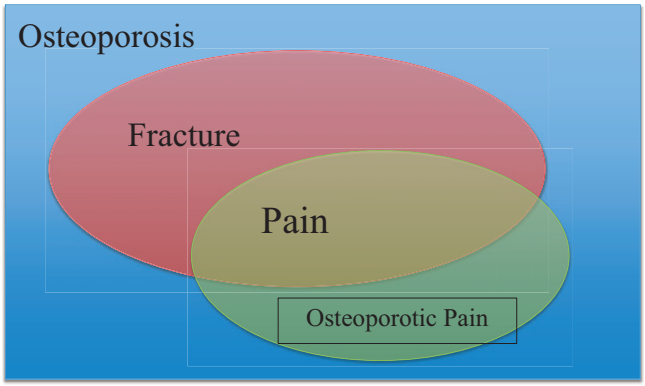

Figure 1. A Venn diagram illustrating osteoporotic pain. Osteoporotic pain is derived from an osteoporotic pathology without fracture or injury.

These changes in DRG can change the pain threshold at the corresponding levels of sensory distribution at the skin (dermatome) and bone (sclerotome). Fig. 3 demonstrates the distribution of the sclerotome of the lumbosacral and pelvic parts of rats, which explains the possible pain induced by pathological DRG[53].

The activation of pain-related molecules upregulates the pain-related pathway at the more central level of the nervous system. In the dorsal horn of the spinal cord, c-Fos protein increases in response to pain stimuli from the peripheral primary afferent nervous system. c-Fos protein is a product of the c-Fos proto-oncogene expression, and it is expressed by noxious and non-noxious stimuli in the postsynaptic neurons of the dorsal horn of the spinal cord[54]. The reported increase in c-Fos in the spinal cord of OVX rats indicates the involvement of osteoporotic pain[55]. Additionally, an estrogen deficiency in osteoporotic patients causes bone loss and alters the spinal serotonergic system by suppressing serotonin (5-HT) receptor expression, which usually plays an important role at the dorsal horn of the spinal cord, resulting in hyperalgesia[56]. These findings such as increased production

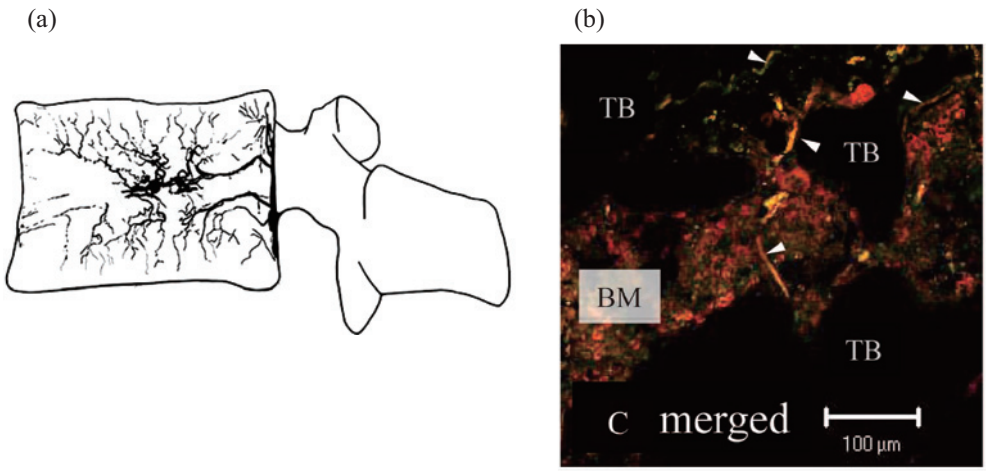

Figure 2. Sensory innervation of a vertebral body (a) The vertebral body is innervated by sensory neurons that are mainly distributed from the posterior wall of vertebrae (adopted and modified from reference 46). (b) An immunofluorescent image of a vertebral section of an ovariectomized rat (merged and immunostained using Tuj-1 [a marker for nerve fibers], and a calcitonin gene-related peptide [an inflammatory pain-related neuropeptide]) (adopted and modified from reference 39). Arrowheads indicate that the sensory fiber innervating the bone marrow (BM). TB: trabecular bone

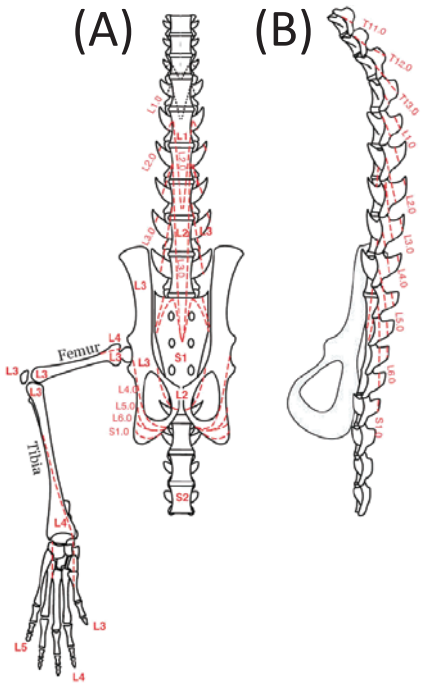

Figure 3. Scheme showing the sclerotome of rats. A: Anteroposterior view, B: lateral view. Segmental distributions of sensory innervation in bones indicate possible reflexion of the altered property of the corresponding sensory neurons (adopted and modified from reference 53).

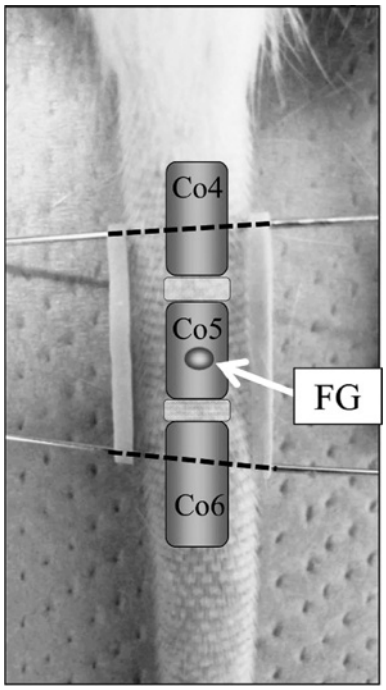

Figure 4. An experiment using the coccygeal vertebrae to investigate the effect of the axial load on sensory innervation (adopted and modified from reference 57). Co: coccygeal, FG: Fluorogold (a retrograde neurotracer) applied onto the dorsal periosteal surface of the Co5 vertebra. The 0.8-mm (diameter) k-wires penetrated the Co4 and 6 vertebrae, and they were connected using experimental rubber bands with a continuous compressive load.

of pain-related channels, receptors, and neuropeptides in DRG and spinal cord as well as change in the local tissue are included in the mechanism of osteoporotic pain.

In addition to these static changes in osteoporotic vertebrae, other dynamic factors can affect osteoporotic pain, e. g., gravity, especially the axial load on the vertebral axis. A previous basic study simulated the axial load using coccygeal vertebrae that were continuously compressed with experimental rubber bands[57] (Fig. 4) to demonstrate the upregulated expression of a neurological injury-related neuropeptide, activating transcription factor 3, as well as CGRPs in the DRG innervating the vertebrae. The authors reported an increased expression of both peptides, so they concluded that osteoporotic pain is caused by a neuropathic factor as well as an inflammatory (nociceptive) one. The result of the study indicates the complicated and chronic mechanism of osteoporotic pain.

Treatment for Osteoporotic Pain

Traditional osteoporosis treatment for pain potentially includes the prevention of possible fracture-induced pain by increasing BMD, which each agent initially aims to achieve. Moreover, each anti-osteoporosis agent has been reported to have a specific pain-related active site, which will be described further in the following sections (Fig. 5).

Antiresorptive agents: Bisphosphonate and denosumab

A bisphosphonate is the most common anti-osteoporosis agent that inhibits osteoclast activity to improve BMD[58,59]. In addition, there have been some reports of using bisphosphonates for pain.

For patients with an osteoporotic fragility fracture, intravenous pamidronate is effective for chronic back pain[60]. Ibandronate is reported to suppress the expression of substance P mRNA and tumor necrosis factor-α in the DRG of a rat model with persistent inflammation[61]. Another bisphosphonate, risedronate, has been reported to suppress the expression of CGRP in the DRG[38] to improve LBP in clinical postmenopausal osteoporotic patients without any evidences of vertebral fractures[38]. Furthermore, an *in vitro* experiment showed the inhibitory effect of risedronate on axonal growth of neurite of pain-related DRG neurons from rat neonates[39], indicating that a bisphosphonate itself can produce an analgesic effect by suppressing peripheral nerve function. Moreover, a third-generation of minodronic acid has been reported to have an analgesic effect by antagonizing purinergic P2X(2/3) receptor function[62]. One study showed that pa-

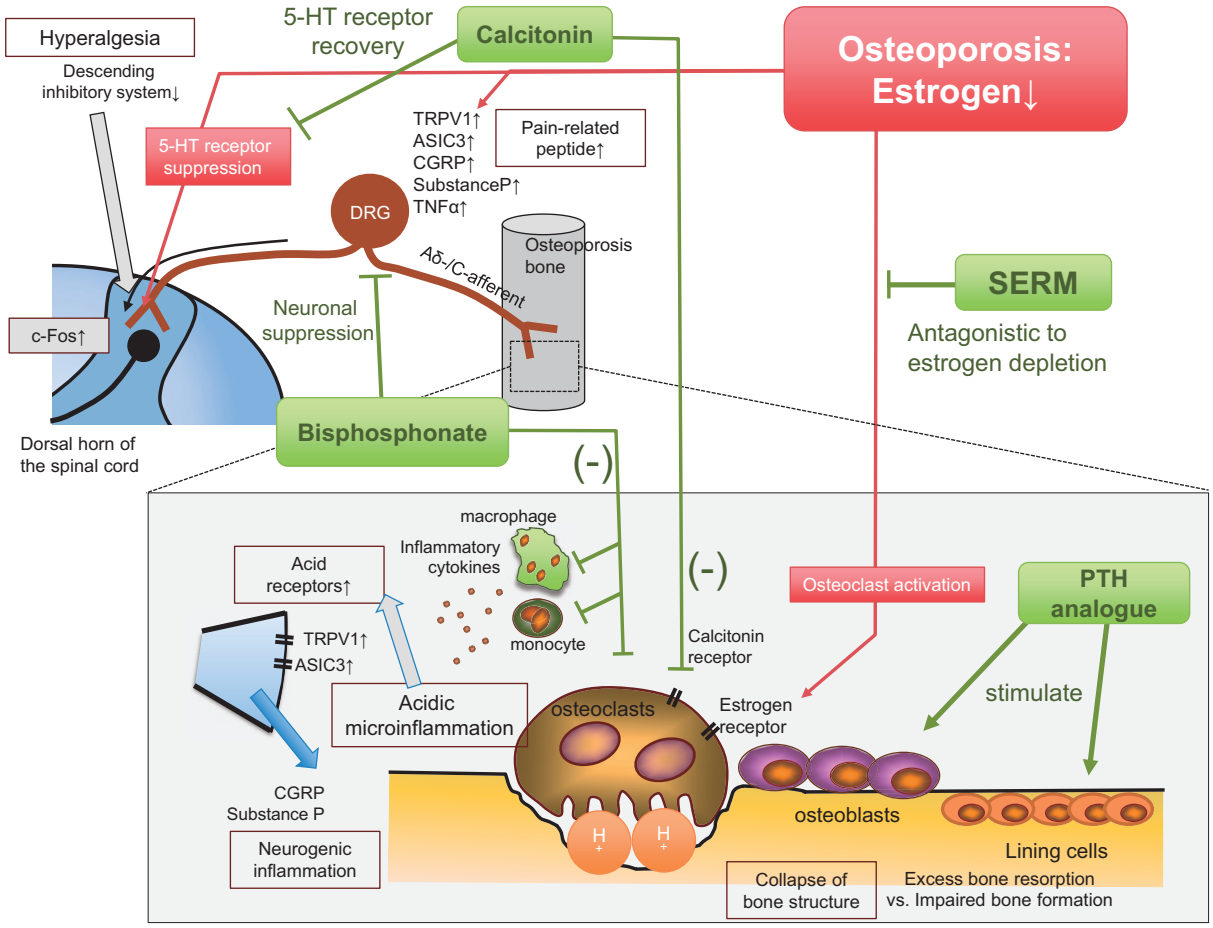

Figure 5. Scheme of osteoporotic pain and the active sites of anti-osteoporotic agents: 5-HT: hydroxytryptamine (serotonin), ASIC: acid-sensing ion channel, TRPV1: transient-receptor potential vanilloid 1, TNF-α: tumor necrosis factor-α, SERM: selective estrogen receptor modulator, PTH: parathyroid hormone

tients treated with daily minodronate showed more pain relief measured on the visual analog scale[63].

A bisphosphonate has effects on other molecules too. Alendronate improves osteoporotic pain by inhibiting TRPV1[52]. In addition, a randomized, controlled trial showed that alendronate produced a stronger analgesic effect than calcitonin in postmenopausal osteoporotic women[64]. Furthermore, combination therapy using risedronate and treadmill exercise in OVX rats showed effective improvement in BMD and decreased expression of pain-related neuropeptides[39], which proves the effect of physical exercise as anti-osteoporotic treatment[65-68].

Recently, another type of anti-osteoporotic agent, denosumab (an anti-receptor activator of nuclear factor-κ B ligand [RANKL] antibody), has been discussed. It has a strong suppressive effect on osteoclasts by inhibiting their differentiation from precursors, and it has a significant effect on BMD improvement[69,70]. RANKL itself is involved in pain pathology[71], and an antagonism against RANKL with denosumab has been reported to improve LBP in patients with osteoporotic pain[72].

Estrogen and Selective Estrogen Receptor Modulator

Administering estrogen or a selective estrogen receptor modulator (SERM) seems reasonable for treating osteoporosis, because the pathology is based on decreased estrogen secretion, which suppresses CGRP expression of DRG[73].

However, SERM has estrogen and estrogen-like effects on bone, and it antagonizes the action of estrogen in the endometrium and breast tissue. A previous study reported that treatment with raloxifene in postmenopausal osteoporotic women showed a marked reduction in musculoskeletal pain[74].

Calcitonin

Calcitonin is an endogenous polypeptide hormone that inhibits bone resorption by osteoclasts[75]. It decreases hyperalgesia in OVX rats by upregulating the activity of the descending serotonergic inhibitory system[76] by recovering the resumption of the synthesis of 5-HT receptors[5,6,77] Another clinical study reported that it has an analgesic effect comparative to morphine[78] with significantly increased plasma β-endorphin levels in patients with postmenopausal osteoporosis[79]. Furthermore, a clinical study indicated that the use of elcatonin better reduced chronic back pain when combined with risedronate for more than 3 months[80], These facts prove the analgesic effect of calcitonin on osteoporotic pain.

Vitamin D

Vitamin D is reported to stimulate osteoblast activity and other effects such as an increase in the intestinal absorption of calcium, and regulation of parathyroid hormone activity, calcium metabolism, and proximal muscle function[81]. Vitamin D-related pain pathways are associated with changes in cortical, hormonal, neuronal, and immunological alterations[82]. Vitamin D alleviates musculoskeletal pain and downregulates inflammatory markers in patients with osteoporosis, especially in those treated with zoledronic acid[83].

Teriparatide

Teriparatide is a human parathyroid hormone analog that induces the formation of new bone by increasing osteoblast generation and stimulating osteoclasts to resorb bone. It significantly induces increased BMD and lowers the incidence of new fractures to achieve improved QOL[84]. Its analgesic effect on osteoporosis-related pain includes a strengthened bone structure, which results in a lower incidence of new microfracture and macrofractures[85]. In a clinical study, teriparatide is reported to significantly reduce low back pain better than risedronate[86]. Because it is a relatively new agent, there is still a lack of evidence using teriparatide to relieve osteoporotic pain, thus this should be investigated in a future study.

Other non-osteoporotic agents

Other non-osteoporotic analgesic agents reportedly have a suppressive effect on osteoporotic pain. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are widely used for chronic pain associated with fragility or traumatic fractures. Additionally, some NSAIDs such as celecoxib and cyclooxygenase-2 selective agents suppress osteoporotic pain by inhibiting carbonic anhydrase II in the osteoclasts, which indicates a possible analgesic effect on osteoporotic pain.

Considering the aforementioned information, anti-osteoporotic treatments are effective for relieving osteoporotic pain by improving bone structure and the condition of the pain-related sensory nervous system.

Conclusions

Osteoporotic pain derived from an osteoporotic pathology is a condition induced by an increase in pain-related neuropeptides in the sensory neurons innervating osteoporotic vertebrae, where activated osteoclasts have more inflammatory conditions that stimulate pain-inducing molecules with acidic inflammatory circumstances. Osteoporosis treatment predominantly aims to increase the BMD of patients to prevent possible fragility fractures, and recent considerable evidence shows that anti-osteoporotic treatment also relieves pain. Physicians should always consider these matters when choosing a treatment strategy that would best benefit patients with osteoporotic pain.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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