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Patchy Osteoporosis in Complex Regional Pain Syndrome

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1. Introduction

Complex regional pain syndrome (CRPS), formerly known as "reflex sympathetic dystrophy" and "causalgia", is a syndrome that refers to a chronic pain condition associated with autonomic disturbances of vasomotor and sudomotor origin (Birklein et al., 1998), along with trophic skin changes and patchy demineralization of the bones (Poplawski et al., 1983). CRPS is classified into type I and II; the former can develop after minor or remote trauma like stroke, spinal cord injury or myocardial infarction (Wasner et al., 1998); the latter can develop after a large peripheral nerve lesion (Janig & Baron, 2003). The syndrome corresponding to what was formerly described as reflex sympathetic dystrophy is now termed as CRPS type I; causalgia is now termed as CRPS type II (Merseky & Bogduk, 1994). Although the mechanism of CRPS has not been elucidated yet, recent studies indicate that it is a complex disorder that involves both the central and peripheral nervous systems (Daemen et al., 1998; Huygen et al., 2001). CRPS pathogenesis is heterogeneous and complex, which makes its treatment challenging. Pharmacological therapies of CRPS include anti-inflammatory drugs, systemic corticosteroid (Kingery, 1997), antidepressants, opioid (Mackey & Feinberg, 2007), anticonvulsants, free-radical scavengers, vasodilatory medication (Perez et al., 2010) and even bisphosphonate agents (Adami et al., 1997; Manicourt et al., 2004; Robinson et al., 2004; Varenna et al., 2000). In addition, vitamin C is recommended to prevent the occurrence of CRPS type I after wrist fracture (Perez et al., 2010).

However, there is yet no single pharmacological agent or treatment algorithm that can resolve all of its heterogenic features. The efficacy for most pharmacological agents remains largely empirical, with the exception of bisphosphonate agents, which are the only agents with proven efficacy for CRPS based on multiple controlled trials (Adami et al., 1997; Brunner et al., 2009; Mackey & Feinberg, 2007;, Manicourt et al., 2004, Robinson et al., 2004, Varenna et al., 2000).

In order to understand how these bisphosphonate agents are useful in CRPS treatment, it is imperative to understand the pathogenesis of patchy osteoporosis in CRPS. This section will first review CRPS, then it will introduce the different experimental animal models. Finally this section will discuss the different treatment agents that have been studied for patchy osteoporosis.

2. Clinical findings of CRPS

2.1 Overview of CRPS

CRPS is painful and it can affect one or more extremities (de Mos et al., 2008). It usually occurs following a physical injury, such as, after fracture or surgery. But spontaneous onset without any triggering factor may occur as well (Veldman et al., 1993). According to a case control study (de Mos et al., 2008), fracture was the most common precipitating injury in 49% of the cases. The mixed etiologies of CRPS are evidenced in its heterogeneous constellation of clinical symptoms. In the acute stages, hallmarks include mechanical hyperalgesia, edema, increased sweating, skin temperature and hair growth (Doury, 1988; Janig & Baron, 2003). After some time, CRPS symptoms progress from a warm to a cold stage, with decrease of skin temperature, formation of skin atrophy and bony osteoporotic changes (van der Laan et al., 1998).

2.2 Diagnosis

CRPS diagnosis is based on its clinical presentation, whereby the diagnostic criteria as developed by the International Association for the Study of Pain (IASP) is most widely accepted (Stanton-Hicks et al., 1995). The IASP task force proposed a definition based on four criteria (Harden et al., 2007). (Table 1) In addition, involuntary movements, muscle spasm, paresis, pseudoparalysis, skin, muscle and bone atrophy, hyperhidrosis and changes in hair and nail growth, can also be observed (Perez et al., 2010; Veldman et al., 1993).

General definition of the syndrome: CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time
To make the clinical diagnosis, the following criteria must be met: 1. Continuing pain, which is disproportionate to any inciting event 2. Must report at least one symptom in three of the four following categories: Sensory: Reports of hyperesthesia and/or allodynia Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) 3. Must display at least one sign at time of evaluation in two or more of the following categories: Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) **4.** There is no other diagnosis that better explains the signs and symptoms
For research purposes, as a rule, CRPS is diagnosed when least one of the symptoms in all of the four symptom categories and at least one sign (observed at evaluation) in two or more sign categories is manifested.

Table 1. Proposed clinical diagnostic criteria for CRPS

Plain radiographs can be used to evaluate the demineralization status, but these show positive findings only in the chronic stages. Three-phase bone scintigraphy is a highly specific and sensitive test for CRPS (Demangeat et al., 1998). The classical finding on bone scintigraphy is increased periarticular activity in the affected limb (Todorovic-Tirnamic et al., 1995). Autonomic function can be tested by infrared thermography. Also, skin temperature differences may be helpful for the diagnosis of CRPS; however, these typical temperature side differences are not static descriptors but comprise changes that can be critically dependent on environmental temperature (Wasner et al., 2001).

2.3 Pathomechanism

The complex cascade of CRPS is postulated to initiate after the sensitization of C-nociceptive fibers and release of neuropeptides, which are linked to vasodilatation and hypersensitization of nerve endings (Guo et al., 2004; Kurvers, 1998; Schurmann et al., 1999). Osteoclasts are also activated and this in turn leads to nociceptor stimulation and sensitization (Mach et al., 2002; Sevcik et al., 2004) leading to a vicious cycle.

A medical history of asthma, migraine, osteoporosis, a recent history of menstrual cycle-related problems or preexisting neuropathies are common pre-existing problems or conditions often concomitantly found in CRPS patients. Therefore finding a common mediator that is both present in these conditions and CRPS could help to reveal the possible triggering factors. The mediators (de Mos et al., 2008; Karacan et al., 2004; Toda et al., 2006) that have been linked among asthma, migraine and CPRS are the neuropeptides calcitonin-gene related peptide, substance P (de Mos et al., 2008), mast cell products (Bradding et al., 2006) and transcription factors such as nuclear factor kappa B (Barnes, 2006; Reuter et al., 2002). Inflammatory cytokines such as interleukin 1, tumor necrosis factor alpha have also been suggested to be common denominators among CRPS, osteporosis and menstrual cycle related disorders, but their definite roles need to be established through continuous studies (Marie et al., 1993; Zarrabeitia et al., 1991).

3. Patchy osteoporosis

3.1 Pathomechanism

Why does bone loss occur in CRPS? Some have postulated that immobilization plays a role in CRPS. Suyama et al, have (Suyama et al., 2002) observed a reduction in BMD 1 to 7 weeks postsurgery with an increase in the number of osteoclasts at 2, 3, and 5 weeks in their CRPS model. They have suggested that one possible mechanism would be the increase of bone resorption with immobilization. Another possible mechanism suggested by others (Whiteside et al., 2006) would be that bone loss in CRPS models may be due to altered nerve signaling and not attributable to limb disuse or reduced mechanical loading associated with pain. Experimental studies have shown that substance P release is involved in the pathogenesis of bony changes induced by CRPS (Gaus et al., 2003).

The exact pathological mechanism of patchy osteoporosis in CRPS and altered nerve signaling is still poorly understood, some consider to be attributable to a regional sympathetic hyperactivity of sympathetic dysfunction (Goldstein et al., 2000; He et al., 2011; Kurvers et al., 1998; Laroche et al., 1997). Sympathetic deregulation causes vasomotor irregularities, and an imbalance between vasoconstriction and vasodilatation, which in turn influences the blood supply to the bone. Other studies have shown that the immune and skeletal systems are closely related to maintain the homeostasis of the bone but when this

interaction is disrupted in CRPS; the balance favors bone loss. This complex cascade is postulated to initiate after sensitization of C-nociceptive fibers and release of neuropeptides, which are linked to vasodilatation, hypersensitization of nerve endings (Guo et al., 2004; Kurvers et al., 1995; Schurmann et al., 1999), and osteoclasts activation, which increase bone resorption, lead to nociceptor stimulation and sensitization (Mach et al., 2002; Sevcik et al., 2004).

3.2 Characteristics

Bone loss in CRPS occurs regionally with loss of the trabecular bone (Bickerstaff et al., 1991; Doury, 1988) with marked bone demineralization observed at the subchondral regions. Epiphyseal regions are predominantly affected, however no narrowing of joint space or bony sclerosis is observed. Recovery of lost bone mineral content is slow and may persist after several years from the initial diagnosis (Nilsson, 1966) and this persistent regional osteoporosis can predispose to other future fractures after minor injuries (Sarangi et al., 1993). Same as the clinical manifestation, studies that have used rat models of CRPS have shown that bone mineral density significantly decrease from the second week (Suyama et al., 2002) and this loss is known to persist for at least 20 weeks (Kingery et al., 2003).

3.3 Radiographic findings

Bone changes can be observed by typical roentgenography but these changes are known to occur only after several months. However periarticular bone loss can be observed in radiograhs of CRPS limbs even within 3 weeks after injury (Bickerstaff et al., 1993). Bone mineral density, measured by dual energy xray abosorpotometry is reduced in the CRPS limbs in a periarticular distribution (Gue et al., 2004).

3.4 Neuropeptides in patchy osteoporosis

Substance P (Bianchi et al., 2008), one of the neuropeptides closely linked to the pathogenesis of CRPS, binds to NK1 receptors of postcapillary venules and causes vasodilation, increasing vascular permeability. The increased activity of this neuropeptide, which are elevated in serum samples from CRPS patients (Schinkel et al., 2006), are deemed to be responsible for the subsequent warmth and interstitial edema observed in CRPS through vasodilation and increased protein extravasation.

This substance P is also postulated to play a role in the development of patchy osteoporosis in CRPS. Studies have shown that substance P is known to stimulate osteoclast formation and active bone resorption through NK1-receptor found in the bone cells (Goto et al., 1998; Liu et al., 2007).

The exact mechanism of how substance P induces bone loss needs to be elucidated; substance P not only has osteoclastic effects but is known to have an osteogenic effect on bone marrow cells and to directly stimulate osteoblastic bone formation (Imai & Matsusue, 2002). The mechanism that favors osteoclastic activation, instead of osteoblastic activation, to result in bone loss in CRPS needs further studies. But in line with the current literature that supports abnormal osteoclastic activation through substance P in CRPS, it is reasonable to theorize that an agent that inhibits substance P would help to reduce osteoclast activation and its ensuing bone loss. This topic was evaluated in a study that used a substance P antagonist LY303870 (Kingery et al., 2003) and determined whether it was efficient in controlling osteoporosis. Although this antagonist was effective in the nociceptive and

vascular abnormalities (Kingery et al., 2003), it proved to be ineffective in preserving bone loss. Its use instead enhanced the widespread osteoporotic effects (Kingery et al., 2003). The dual and dichotomous roles of substance P in maintaining bone integrity in CRPS needs to be further elucidated.

Substance P activation also leads to the over-expression of the inflammatory cytokines (Wei et al., 2009). Some of these cytokines play a role in the development of patchy osteoporosis in CRPS. Nerve growth factor is one of the cytokines activated by the substance P, and its activity leads to nociceptive sensitization, enhanced osteopenia with increased cytokine content (Sabsovich et al., 2008). Tumor necrosis factor alpha is another pro-inflammatory cytokine postulated to play a role in the development of CRPS changes after trauma and its expression is increased in CRPS patients (Huygen et al., 2001). Although the increased level of the tumor necrosis factor is an important mediator of regional nociceptive sensitization, it does not contribute to the enhanced bone loss (Sabsovich et al., 2008).

4. Current laboratory research in osteoporosis related with CRPS

4.1 Overview of laboratory research in CRPS

In order to unravel the mechanisms underlying osteoporosis in CRPS, many animal models have been introduced. There are two broad categories of mechanisms underlying CRPS: (1) peripheral mechanisms: CRPS is primarily an inflammatory disease in the periphery (CRPS I) or a consequence of nerve damage (CRPS II), (2) central mechanisms that involve reorganization of the somatosensory, somatomotor and autonomic systems in the central nervous system triggered by a peripheral input (Drummond et al., 2001; Turner-Stokes, 2002; Wasner et al., 2003). Both the peripheral and central nervous systems play a role in the pathogenesis of CRPS. The peripheral mechanisms includes immune cell mediated inflammatory, autoimmune inflammatory processes, neurogenic inflammation and tissue hypoxia. (Daemen et al., 1998a; Daemen et al., 1998b; Kingery et al., 2003b; Kurvers et al., 1998; Offley et al., 2005; Schurmann et al., 2000). However, the amount of contribution of these two mechanisms and how they interact with each other to manifest in CPRS has not been determined yet. Keeping in mind of these two different mechanisms, and that CRPS can be either type I or II, several animal models that represent these features have been introduced but because of the inherent heterogenic features of CRPS, there is no absolute model that shows and reproduces all CRPS features.

Depending on the presence of peripheral nerve injury, three animal models will be discussed. For CRPS type I, the tibia fracture model and chronic ischemic model will be presented (Coderre et al., 2004; Guo et al., 2006; Ludwig et al., 2007). The chronic constriction injury (CCI) model of the sciatic nerve will be presented for CRPS type II (Bennett and Xie, 1988). Choosing the type of experimental model may depend on the objective of the research or researcher's habit. The methodologies of these different animal models are discussed to provide detail reference for the readers.

4.2 Tibia fracture and cast rat model

Tibia fracture and cast rat model had been introduced for the animal model of CRPS type I, and is popularly used in laboratory studies (Guo et al., 2004; Guo et al., 2006; Sarangi et al., 1993). The method of induction for tibia fracture model is as follows: the hind limb of rat is wrapped in stockinet and the distal tibia is fractured. The hind limb is then wrapped in casting tape with the hip, knee, and ankle in flexed position. The cast extends from the

metatarsals of the hindpaw up to a spica formed around the abdomen. At 4 weeks the cast is removed. This rat model shows changes in volume, temperature, nociception and osteoporosis of the hind limb.

This tibia fracture and cast model has several benefits. Most of all, this animal model represents the CRPS type 1. This model is theorized to induce post-junctional facilitation of substance P signaling. Because this model reproduces the typical symptoms of CRPS such as mechanical allodynia, paw thickness (edema), vasodilation and bone mineralization, it is commonly used in research studies that focus on the treatment and pathomechanism of CRPS. The exact mechanisms of how the intact peptidergic primary afferent neurons are activated after fracture and casting has not elucidated yet. Although there are many studies that have used this model to investigate the pathomechanism of CRPS type I, there are yet no studies that have exclusively focused on patchy osteoporosis with this model.

4.3 Ischemic – Reperfusion injury model

Another typical animal model for CRPS type I is the chronic ischemic model (Coderre et al., 2004; Xanthos et al., 2004). The femoral artery is dissected and ligated above the origin of the profunda femoris artery for the 3 hours with a small polyethylene tube. Ligation is performed tightly with the vessel walls pressed together and complete arterial occlusion is ensured under microscope. This method completely interrupts the arterial blood supply to the lower leg and hindpaw. The wound is closed by means of five sutures put on the skin. To prevent thrombosis of the artery, two subcutaneous injections of heparin are given subcutaneously, one at the beginning and one at the end of the period of ischemia. This ischemic injury shows change of skin temperature, spontaneous pain behavior, mechanical and cold allodynia and edema, and are consistent with CRPS type I.

Previous research revealed that CRPS type I may depend on chronic tissue ischemia that is dependent on, or exacerbated by, an indirect sympathetic–afferent coupling with an intervening role of enhanced a-adrenoceptor mediated vasoconstriction. The ischemia-reperfusion injury model is another animal model for CRPS type I that is produced based on this mechanism.

4.4 Chronic constriction injury (CCI) model

The CCI model; first introduced by Bennett and Xie (1998); is a classic model for CRPS and has been commonly used in various studies. In this model the common sciatic nerve is exposed at the level of the middle of the thigh by blunt dissection through the biceps femoris. Proximal to the sciatic's trifurcation, about 7 mm of nerve is freed from adhering tissue and 4 ligatures are loosely tied loosely around it with 1 mm spacing. The length of the ligated nerve is approximately 4-5 mm long.

This model is known to represent CRPS type II. This model shows changes of skin thickness, temperature, mechanical sensitivity and bony changes such as patchy osteoporosis. This model has been the model most frequently used to study the patchy osteoporosis in CRPS. Patchy osteoporosis resembling that of CRPS can also be induced by the sciatic nerve trans-section (Kingery et al., 2003a; Kingery et al., 2003b). This model is also used for studies on CRPS type II. However, the CCI model had shown several benefits for weight bearing than the sciatic nerve trans-section model. Many of the laboratory researches on patchy osteoporosis in CRPS are mostly based on the CCI model.

5. Treatment of patchy osteoporosis in CRPS

5.1 Overview of medication for patchy osteoporosis

Pharmacological therapy of CRPS encompasses a wide spectrum of medication; from anti-inflammatory drugs, systemic corticosteroid (Kingery, 1997), antidepressants, opioid (Mackey & Feinberg, 2007), to anticonvulsants agents. Because the activation of bony osteoclasts is known to play significant role in CRPS pain generation, it is not surprising that aside from these central pain modulating medications, bone modulating agents are used in CRPS. These agents are known not only to alleviate pain but also to reverse and inhibit CRPS associated osteopenia (Whiteside et al., 2006). The two bone modulating agents in reference are calcitonin and bisphosphonate agents.

5.2 Calcitonin

Calcitonin has been traditionally used in bone pathologic conditions due to its efficacy on microvasculature, bone resorption and analgesic action (Friedman & Raisz, 1965). The use of calcitonin in CRPS has been shown through its possible mechanism in controlling bone pain. The results of calcitonin in clinical practice are still controversial; while some have questioned the efficacy (Kingery, 1997), others support its efficacy in CRPS pain (Perez et al., 2001). A recent review analysis also describes positive results for calcium-regulating drugs, including calcitonin, administered to CRPS patients (Fofouzanfar et al., 2002). Although calcitonin has some efficacy in pain, range of motion, with a rapid onset of action (Gobelet et al., 1992), whether its use has effect on the patchy osteoporosis in CRPS has not been validated through animal or clinical studies.

5.3 Bisphosphonate

5.3.1 Mechanism of bisphosphonate through experimental studies

Bisphosphonates are analogues of inorganic pyrophosphates and are inhibitors of bone resorption. They act on the bone and inhibit the action of osteoclasts, thereby limiting bone resorption. Due to this mechanism, they have been found to be effective in the treatment of osteoporosis and other bone conditions. Bisphosphonates have been used traditionally for pathological bone conditions, such as osteoporosis, Paget's disease, cancer related bone pain, metastatic cancer, tumor related hypercalcemia, myeloma and vertebral fracture (Adami et al., 1997; Brunner et al., 2009; Bonabello et al., 2001; Fleisch, 1997; Fulfaro et al., 1998; Fulfaro et al., 2005). In CRPS, bisphosphonates have shown more promising results than calcitonin and many studies supports itse use in CRPS (Adami et al., 1997; Breuer et al., 2008; Manicourt et al., 2004; Robinson et al., 2004; Varenna et al., 2000), in fact, bisphosphonates are the only pharmacological agents with beneficial analgesic results confirmed through placebo controlled trials (Adami et al., 1997; Manicourt et al., 2004; Varenna et al., 2000). However, there is yet no consensus on the optimum dosage, frequency, and duration of treatment in CPRS.

The role of bisphosphonate in the regulation of the substance P and hyperalgesia has been shown in an experimental study using ibandronate (Bianchi et al., 2008), a bisphosphonate agent. As stated earlier, substance P sensitizes afferent fibers and increases the sensitivity to nociceptive stimuli. It has been hypothesized that ibandronate prevents proton production by osteoclasts, and reduce the activation of specific ion channels and consequent production of substance P by primary afferents (Bianchi et al., 2008), thereby limiting hyperalgesia and bone loss. Also bony calcium homeostasis can influence the Ca^{2+} dependent endogenous regulation

of pain sensitivity (Bonabello et al., 2001). Bisphosphonates can effect bone tissue by alternation of the calcium/phosphate product. It is postulated that it is through these mechanisms that bisphosphonate administration inhibits the release of neuropeptides that are responsible for the pain and other vasomotor changes in CRPS. Also, it is postulated that it is through these same mechanisms that bisphosphonate agents are useuful in limiting bone loss.
In fact, animal studies have shown bisphosphonates are effective in preserving CRPS associated bone loss. Chronic administration of zoledronate acid can lead to increased BMD in CCI animal models (Whiteside et al., 2006). The efficacy of alendronate in limiting bone loss in CCI rat model has been shown in a recent study (Im et al., 2010). In both the acute and chronic stages after CCI induction, alendronate treatment preserved bone mass with sustained efficacy in bone preservation, which was demonstrated through in vitro tibia BMD and tibia strength results.

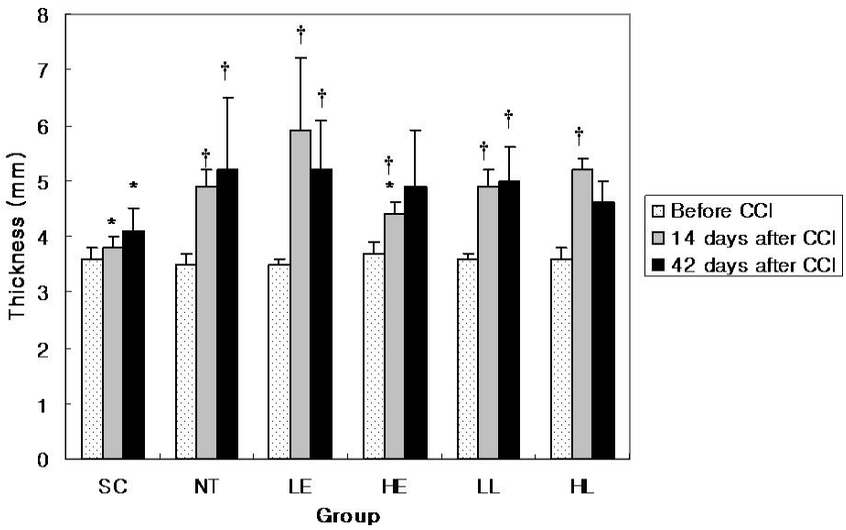
5.3.2 Clinical studies of bisphosphonate

The role of bisphosphonates in CRPS is well supported by many clinical studies but most were focused on their efficacies in pain. There are already many reports that have advocated the use of bisphosphate agents for CRPS related hyperalgesia and pain (Adami et al., 1997; Breuer et al., 2008; Mackey & Feinberg, 2007; Manicourt et al., 2004; Robinson et al., 2004; Varenna et al., 2000). Results from clinical studies have postulated that alendroate reduces local bone resorption and is effective in CRPS pain by its nociceptive effects in bone. (Adami et al., 1997; Manicourt et al., 2004). For example, Varenna et al. have shown in their randomized, double blind placebo controlled study that a 10 day intravenous clondronate course is effective in the treatment of CRPS (Varenna et al., 2000). A recent clinical study of ibandronate, a potent bisphosphonate agent, has shown that its analgesic effects (Bianchi et al., 2008). However, most studies focused on their analgesic effects for bone pain rather than on their bone preserving effects.
Bone loss in CRPS predominate the chronic stages of CRPS and is accompanied by trophic changes. This patchy bone loss is difficult to reverse and as stated earlier, can lead to fractures even from trivial stress. Therefore, alongside with the management of pain, management of CRPS associated patchy osteoporosis is important to prevent such detrimental consequences.
The efficacy of bisphosphonate agents in patchy osteoporosis have been shown in some studies. A theraupetic role of bisphosphonates on clinical and densiometric recovery was shown in transient hip osteoporosis; a condition considered by many to be a prestage of CRPS (Mailis et al., 1992) with similar features commonly observed in CRPS. Administration of bisphosphonate in transient hip osteoporosis led to the recovery of bone densiometry along with complete pain resolution (Varenna et al., 1996). Similary, the efficacy of bisphosphonate therapy in the recovery of bone mineral content was also shown in CRPS (Adami et al., 1997). Adami et al. used intravenous alendronate and evaluated their pain, tenderness, swelling and bone mineral content of the affected arm. Although a change of bone mineral content was not observed in the unaffected side, the affected side bone mineral content rose significantly in comparison to baseline values. These results show that bisphosphonates are helpful in limiting CRPS associated pathcy osteoporosis.

5.4 Dosage and administration of bisphosphonate in patchy osteoporosis

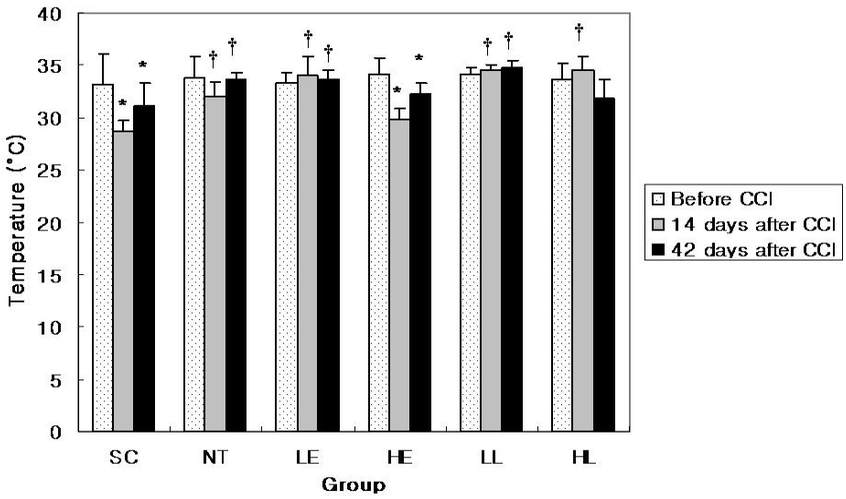
With bisphosphonates as the agent with much clinical and experimental evidence to support its use in CRPS, the best dosage and timing of administration is an issue that has gained much focus. A study of dosage differentiation was previoulsy carried out with doses of pamidronate

varying from 30mg/day to 1mg/Kg/day, provided for three consecutive days. However no dose correlation was observed in these clinical trials (Maillefert et al., 1995). In contrast, some animal studies have shown a dose dependent antinociceptive effects (Bonabello et al., 2001)with pamidronate and clodronate. Etidronate and alendronate have not shown this dose dependent response and their analgesic effects were observed only with the highest dose.
Similar to these experiments, in their study with CCI models, Im et al. has shown that different dosage and time of administration of oral alendronate leads to different results in bone mineral density of the tibia and tibia bone strength (Im et al., 2010). The high dosage group received 1mg/kg/day while the low dosage group received 0.1mg/kg/day. To determine whether the time of administration lead to significant differences, the high and low dosage groups were further divided into the early and late administered group. The early group received alendronate treatment immediately after CCI induction, while the late group received alendronate at the 14th day. Both groups received alendronate treatment until the 6th week of CCI induction. The results showed that different dosages and time of administration leads to different efficacies across different CRPS signs. While the hind paw thickness and temperature were significantly reduced only with high dosage administered immediately after CCI induction (Fig. 1, Fig. 2), bone strength and bone mineral density was significantly increased in the high dosage group, with both in the early and late admistered group (Fig. 3, Fig. 4). Bone loss in CRPS becomes manifest in the chronic stages and is known to progress over several months. Because bone loss predominates the later course of CRPS, the authors suggested that the high dosage alendronate, whether admnistred in the early or late course of CRPS, can show significant efficacy in bone metabolism.



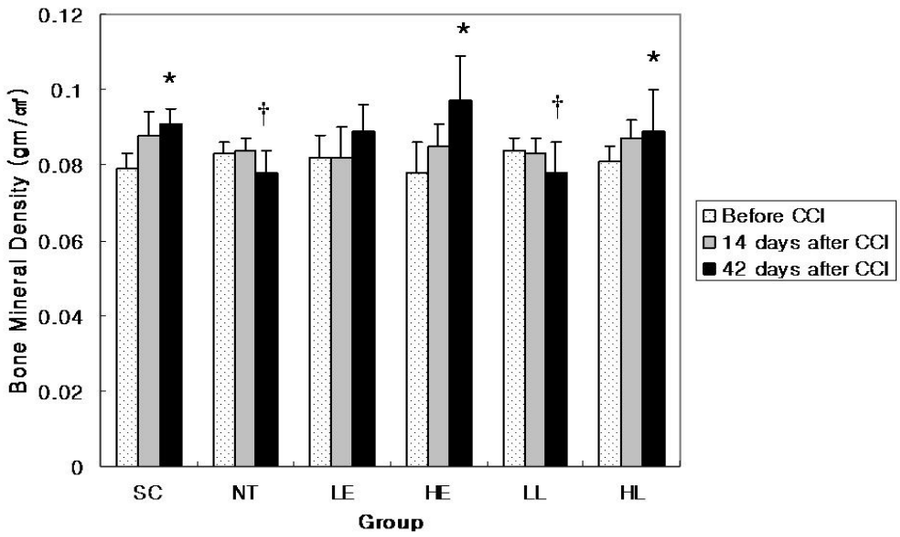
*P<0.001 as compared with NT group, †P<0.001 as compared with SC group.
Abbreviations: CCI, chronic constriction injury; SC, sham control; NT, no treatment; LE, low dosage early treatment; HE, high dosage early treatment; LL, low dosage late treatment; HL, high dosage late treatment

Fig. 1. Efficacy of oral alendronate in different dosage and time of administration in dorsal-ventral thicknesses of the affected hind-paw from Sprague-Dawley rats. (Adapted from Im, S., Lim, S.H., Lee, J.I., Ko, Y.J., Park, J.H., Hong, B.Y. & Park, G.Y. Effective dosage and administration schedule of oral alendronate for non-nociceptive symptoms in rats with chronic constriction injury. Journal of Korean Medical Science 2010; 25(6): 938-944)



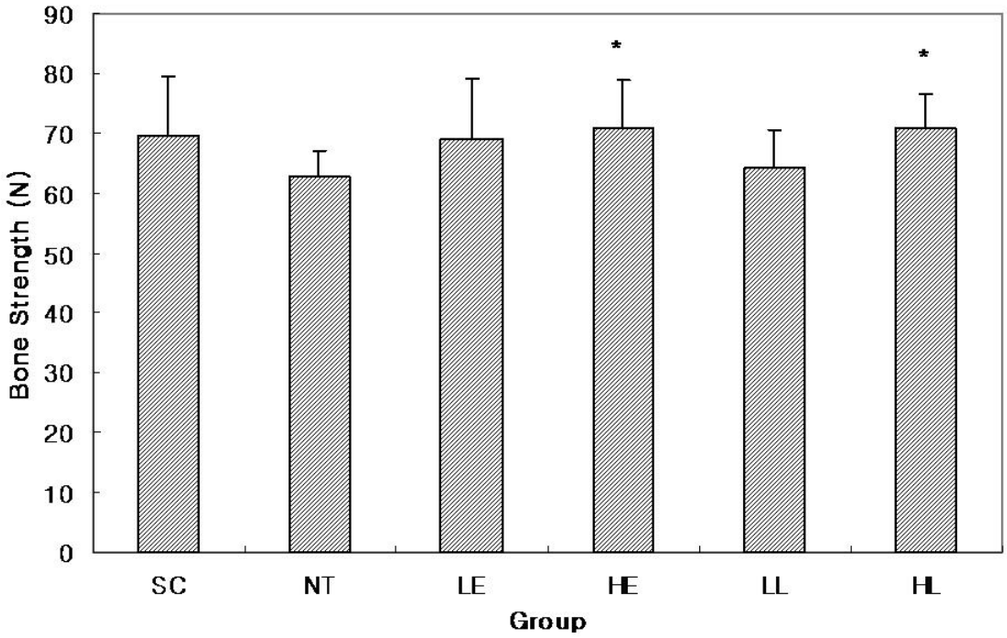
*P<0.001 as compared with NT group, †P<0.001 as compared with SC group.
Abbreviations: CCI, chronic constriction injury; SC, sham control; NT, no treatment; LE, low dosage early treatment; HE, high dosage early treatment; LL, low dosage late treatment; HL, high dosage late treatment

Fig. 2. Efficacy of oral alendronate in different dosage and time of administration in skin temperature of the affected hind-paw from Sprague-Dawley rats. (Adapted from Im, S., Lim, S.H., Lee, J.I., Ko, Y.J., Park, J.H., Hong, B.Y. & Park, G.Y. Effective dosage and administration schedule of oral alendronate for non-nociceptive symptoms in rats with chronic constriction injury. Journal of Korean Medical Science 2010; 25(6): 938-944)



*P<0.001 as compared with NT group, †P<0.001 as compared with SC group.
Abbreviations: CCI, chronic constriction injury; SC, sham control; NT, no treatment; LE, low dosage early treatment; HE, high dosage early treatment; LL, low dosage late treatment; HL, high dosage late treatment

Fig. 3. Efficacy of oral alendronate in different dosage and time of administration in BMD of the affected tibia from Sprague-Dawley rats. (Adapted from Im, S., Lim, S.H., Lee, J.I., Ko, Y.J., Park, J.H., Hong, B.Y. & Park, G.Y. Effective dosage and administration schedule of oral alendronate for non-nociceptive symptoms in rats with chronic constriction injury. Journal of Korean Medical Science 2010; 25(6): 938-944)



*P<0.001 as compared with NT group
†P<0.001 as compared with SC group.
Abbreviations: CCI, chronic constriction injury; SC, sham control; NT, no treatment; LE, low dosage early treatment; HE, high dosage early treatment; LL, low dosage late treatment; HL, high dosage late treatment

Fig. 4. Efficacy of oral alendronate in different dosage and time of administration in bone strength of the right tibia from Sprague-Dawley rats, obtained after the rats were sacrificed. (Adapted from Im, S., Lim, S.H., Lee, J.I., Ko, Y.J., Park, J.H., Hong, B.Y. & Park, G.Y. Effective dosage and administration schedule of oral alendronate for non-nociceptive symptoms in rats with chronic constriction injury. Journal of Korean Medical Science 2010; 25(6): 938-944)

Despite these results, studies that evaluate on the appropriate human dosage of bisphosphonates to alleviate CRPS associated bone loss are warranted in future studies. Although previous studies have shown variable efficacy of bisphosphonate agents with different dosages and time of administration for the different signs of CRPS, the dosage administered in the high dosage group was approximately 5–6 times higher than standard clinical dosages, thus, the high dosage used in experimental studies poses potential problems to directly administer to humans.

Responses to bisphosphonates can vary depending on which agent is used and also on when and how these agents are administered. More experimental studies that asses the efficacy of different bisphosphonate dosages and time of administration in pain and temperature are needed to translate these findings to clinical usage. Also, it would be of interest to determine if prophylactic high dosage bisphosphonate administration in CRPS are helpful in limiting the bone loss that continues until the later stages of CRPS. Finally long term follow-up clinical data are needed to evaluate the efficacy of bisphosphonates in limiting bone loss through objective evidence from bone densiometry and bone markers.

5.5 Neuropeptide modulators

Because the pathogenesis of patchy osteoporosis is related to neurogenic inflammation and the production of substance P, many studies that targeted these neuropeptides have been published. As stated earlier, substance P activation also leads to the over-expression of the inflammatory cytokines (Wei et al., 2009), for example, nerve growth factor is one of the cytokines that leads to osteopenia. The use of a nerve growth factor antibody not only reduced nociception but to a modest degree, maintained further bone loss in the distal trabecular bone (Sabsovich et al., 2008). Pentoxifylline, a cytokine inhibitor, was used to evalute its effect in trabecular bone loss (Wei et al., 2009). Pentoxifylline had significant effects in the fracture induced up-regulation of inflammatory cytokines and reversed nociceptive sensitization and vascular abnormalities. However, it had insignificant effects on bone architecture as measured by microcomputed tomography in a tibia fracture model of CRPS. Although pentoxifylline treatment can induce osteoblastic differentiation, it had no significant effect on trabecular bone loss (Sabsovich et al., 2008).

Although the exact mechanism and relationship of osteoclastic activation, with subsequent activation of substance P and inflammatory cytokines needs further evaluation, most experimental studies have shown that only the agents that directly inhibit bone resorption through osteoclast inhibition have efficacy in preserving CRPS associated bone loss. To date, bisphosphonate agents are ideal for controlling the pain and for limiting bone loss in CRPS.

6. Conclusion

The main focus in CRPS both in clinical and experimental settings has been focused on hyperalgesia and vasomotor symptoms. The symptoms are manifest from the early stages of disease, are profound and affects patients' quality of life. In contrast, patchy osteoporosis in CRPS are not apparent until the later stages, and bone loss rarely causes any symptoms until a minor trauma leads to unexpected fractures. Despite the different clincal manifestations of hyperalgesia and osteoporosis, and the tendency to divide CRPS into different stages, all the signs of CRPS are in continuum and dependent on one another; one sign of CRPS does not stand alone and one can not exist without the other, therefore simply aiming the treatment focused on one aspect can not limit the heterogenic features of CRPS. Vasomotor and sudomotor signs and patchy osteoporosis in CRPS are triggered through similar pathways and neuropeptides are the mediators that link them together. To date, bisphosphonates in high dosages have been used with the aim to control these neuropeptides through osteoclastic modulation. Future studies and clinical trials are warranted for the treatment of CRPS patchy osteoporosis.

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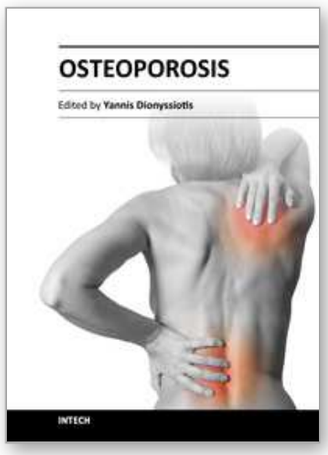

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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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