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Osteoporotic Pain

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1. Introduction

Pain derived from musculoskeletal disorders play a major role in the health profile of the general population (Badley et al., 1994). Generally, osteoporosis patients experience several kinds of pain, including LBP: pain derived from external injury such as from fractures of the compressed vertebrae or femoral neck, and pain from internal consequences of the osteoporotic state without injury, which has been reported to account for pain in 89% of menopausal osteoporosis patients (Scharla et al., 2006). The exact mechanism for that pain still remains unknown, but some studies have tried to clarify that. In a previous study in which SPECT RI, bone scintigraphy, and X-rays were used, pain from injury was reported to be caused by collapsed vertebral bodies and degenerated intervertebral disc and facet joints (Ryan et al., 1992), which proved one of the evidence of injury-derived pain. The injury-derived pain in osteoporosis patients tends to turn into acute pain, whereas the non-injury-derived pain tends to take a chronic course, among which the latter must be sought for its pathogenesis. Here, we define pain derived from osteoporosis without any fractures or injuries as "osteoporotic pain." In this chapter, we review osteoporotic pain by showing the association between its possible mechanism and treatment. Regarding the detailed pharmacological character and use of each anti-osteoporosis agent, please refer to the other appropriate chapters.

2. Mechanism and pharmacological management of osteoporotic pain

2.1 Overview

In the bone tissue, nociceptors respond to mechanical, thermal, and chemical stimuli. Injury or inflammation results in the release of a variety of chemical mediators (e.g., prostaglandins, cytokines, and growth factors), which not only stimulate osteoclast activity but also activate nociceptors and decrease their threshold for activation (Haegerstam, 2001; Payne, 1997). The alteration in bone turnover leads to microfractures of bone, which may be one of the possible accepted origins of osteoporotic pain. Furthermore, other mechanisms for osteoporotic pain are reviewed in this section.

Menopause is well known to be one of the essential causes of osteoporosis in humans (Albright, 1989), and the most important change after menopause is the depletion of estrogen that regulates the expression of various genes (Beato, 1989), which leads to a decrease in the amounts of gene products, including receptors and peptides, required for

modulation of nociceptive transmission. Furthermore, estrogen modulates osteoclast formation both by directly suppressing Receptor activator of NF-κB ligand (RANKL)-induced osteoclast differentiation and by down-regulating the expression of osteoclastogenic cytokines from supportive cells (Shevde, et al., 2000).

In basic studies, ovariectomized (OVX) rats are often used as well-known osteoporosis pathological model, which exhibit the same hormonal changes observed in humans with osteoporosis. Regarding pain perception, a significant reduction in the latencies of tail withdrawal from hot water (Forman et al., 1989) and long-term formalin-induced licking has also been reported to be increased in OVX rats (Franceschini et al., 1983), and because of this, OVX is thought to induce hyperalgesia in rats. These increased pain perception should be another reason for the osteoporotic pain.

Osteoporosis treatment against pain itself potentially includes the prevention of possible fracture-induced pain by increasing bone mass density (BMD), which each agent originally aims to acquire. Furthermore, each anti-osteoporosis agent has been reported to have its own specific pain-related active site, which will be described further in the following sections.

In this section we will review the possible mechanism underlying osteoporotic pain with the relation to the osteoporosis agents, details of which have been obtained from several studies in which some of the mechanisms overlap and remain unclear, that tells us the several sources of osteoporotic pain in the central/peripheral nervous system for its manifestation in local sites of osteoporosis. Fig. 1 below shows us the general view of several sources of osteoporotic pain in the central/peripheral nervous system. Regarding the detail of the each agent, please refer to the following subsections.

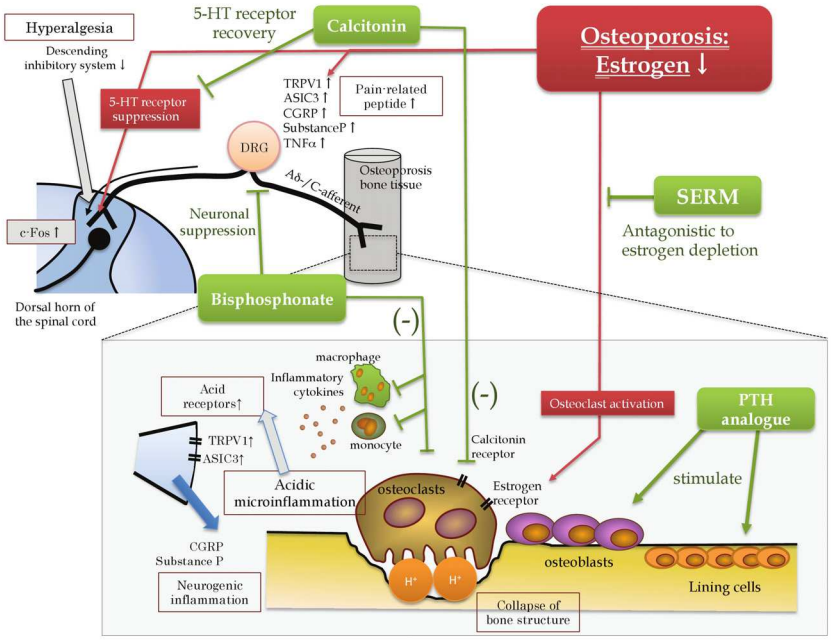

Fig. 1. Possible mechanism underlying osteoporotic pain. Green boxes show the roles of osteoporosis agents.

2.2 Calcitonin

Calcitonin is a polypeptide hormone involved primarily in the regulation of calcium homeostasis; it is secreted into the general circulation by the parafollicular C cells of the mammalian thyroid gland, and regulates the blood calcium concentration and bone metabolism by suppressing the activity of osteoclasts by binding calcitonin receptor on them. Thus, it reduces the blood calcium concentration in hypercalcemia and improves bone mass in osteoporosis. It is usually administered via a subcutaneous injection, and its analgesic effect as well as the resulting increase in bone mineral density (BMD) has been observed and reported in clinical situations; some RCT studies showed that calcitonin produced an analgesic effect in patients with osteoporotic vertebral compression fractures (Knopp et al., 2005; Lyritis et al., 1999), reflex sympathetic dystrophy(or Complex regional pain syndrome: CRPS) (Gobelet et al., 1992) , and cancer pain (Roth & Kolarić, 1986).

The analgesic effect of calcitonin is reported to be related to the serotonergic system in the spinal cord: a presynaptic serotonin (5-HT)-induced inhibition of excitatory glutamatergic transmission evoked monosynaptically by stimulating C-afferent fibers in the substantia gelatinosa (SG) neurons existing in the lamina II of the spinal dorsal horn (Fig. 2). Incidentally SG neurons play an important role in the modulation of nociceptive transmission from the periphery to the central nervous system (CNS), in which nociceptive information is transmitted by fine myelinated Aδ-afferent and unmyelinated C-afferent fibers terminating preferentially (Kumazawa & Perl, 1978; Light et al., 1979; Sugiura et al., 1986; Sugiura et al., 1989; Yoshimura & Jessell, 1990; Yoshimura & Jessell, 1989).

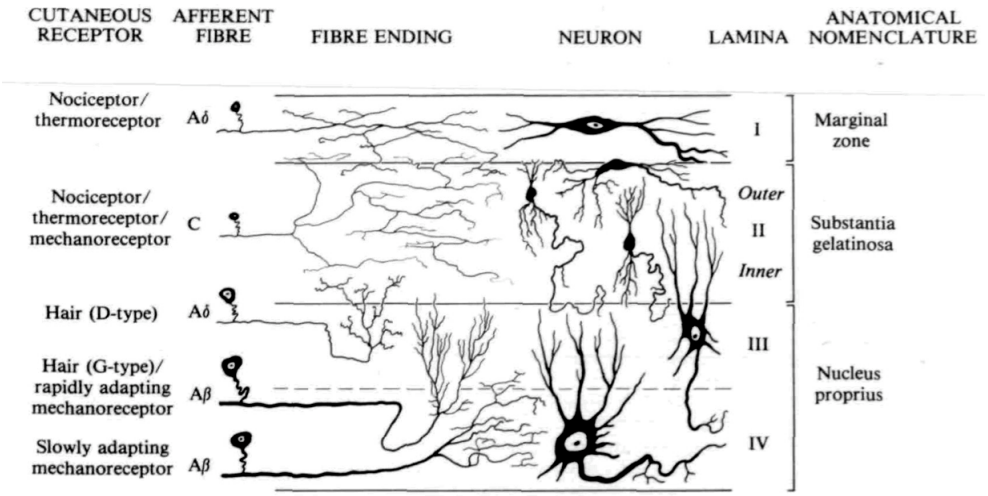

Fig. 2. Schematic diagram of the neuronal organization of the superficial dorsal horn in the spinal cord and the afferent input to the same. Substantia gelatinosa exists in lamina II, in which myelinated Aδ-afferent fibers and unmyelinated C-afferent fibers terminate preferentially (Cervero & Iggo, 1980)

In osteoporosis, estrogen deficiency not only causes bone loss but also alters the spinal serotonergic system by suppressing 5-HT receptor expression, which usually plays an important role in descending pain inhibitory system; this results in hyperalgesia. In other words, the hyperalgesia observed in the osteoporotic model is, at least in part, mediated by

disinhibition of pain transmission in the spinal cord. Calcitonin recovers these changes in the dorsal horn leading to a resumption of synthesis of 5-HT receptors followed by the recovery of descending inhibiting pathway; this in turn produces the analgesic effect (Ito et al., 2000).

Other previous studies demonstrate the analgesic effect of calcitonin. One basic study shows that calcitonin decreased hyperalgesia in ovariectomized rats by upregulating the activity of the descending serotonergic inhibitory system (Takayama et al., 2008) , and another clinical study reported that it produced an effect comparative to morphine analgesia (Martin et al., 1995) . Furthermore, calcitonin has been reported to significantly increase the plasma β-endorphin levels in patients with postmenopausal osteoporosis (Ofluoglu et al., Akyuz, Unay, & Kayhan, 2007) . These facts prove the analgesic effect of calcitonin in osteoporotic pain.

Additionally, calcitonin is administered subcutaneously in the clinical situation. That makes easier to use for those osteoporotic pain patients with symptoms of gastroesophageal reflux disease and in elderly patients with kyphosis (Yamane et al., 2011) or with low medical compliance, which often makes it difficult to use other internal agents.

2.3 Bisphosphonate

Bisphosphonate (BP) regulates bone turnover by suppressing osteoclast activity, and its anti-fracture efficacy has been reported in osteoporosis patients. BP exerts its anti-osteoporosis effects by binding to hydroxyapatite in the bone tissue, inhibiting osteoclast activity, and inducing apoptosis of osteoclasts. Recently, it has been reported to produce suppressive effects on monocytes and macrophages as well; this in turn leads to the suppression of more acute conditions (Roelofs et al., 2010)

Clinically BP has the potential to prevent or relieve back pain in patients with spinal osteoporosis. For instance, risedronate produced an analgesic effect on osteoporosis patients with chronic low back pain who had no evidence of fractures (Ohtori et al., 2010). Alendronate resulted in a rapid decrease in back pain and improvement in QOL in postmenopausal women with osteoporosis (Iwamoto et al., 2010). In addition, an RCT study showed that alendronate produced a stronger analgesic effect than calcitonin in postmenopausal osteoporotic women (J. Iwamoto et al., 2010).

Recent studies tell us that several factors are involved in the analgesic mechanism of BP. First, it is caused by the modulation of pain-transmitting neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) and inflammatory cytokines such as tumor necrosis factor (TNF)-α. Regarding the effect on pain-related neuropeptide, ibandronate is reported to suppress the expression of substance P mRNA and TNF-α in dorsal root ganglia (DRG) in a rat model of persistent inflammation (Bianchi et al., 2008). Here estrogen has reported to suppress CGRP production in DRG using OVX rats (Yang et al., 1998); hence, it is acceptable that estrogen deficiency in osteoporosis patients induces increased CGRP production. Herein we demonstrated that risedronate has suppressed the CGRP production (Fig. 3).(Orita et al., 2010).

Also, transient-receptor potential vanilloid 1 (TRPV1) is also upregulated in the DRGs of OVX rats (Orita et al., 2010). TRPV1 is a ligand-gated non-selective cation channel preferentially expressed in small-diameter primary afferent neurons (Tominaga et al., 1998). It responds to capsaicin, noxious heat and acid. Osteoporotic osteoclasts degrade bone minerals by secreting protons through the vacuolar H^+-ATPase creating local acidic

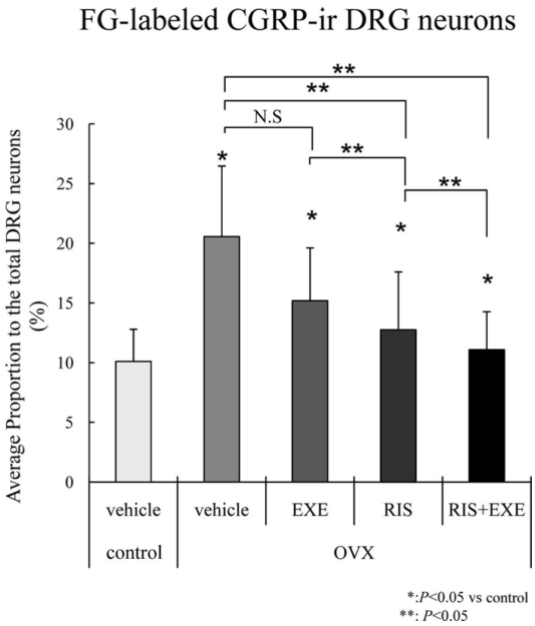

Fig. 3. CGRP production in ovariectomized (OVX) rats. Average CGRP production is suppressed in the BP-treated group than in the vehicle-treated OVX group or physical exercise (EXE)-only treated group. TheCGRP production was mostly suppressed by the combination of RIS and EXE (described in section 3) (Orita et al., 2010).

microenvironments by inflammation (Rousselle & Heymann, 2002; Teitelbaum, 2000), which should evoke the stimulation of TRPV1. Furthermore, this acidic microenvironment stimulates acid-sensing ion channels (ASICs). Increased activities of osteoporotic osteoclasts also lead to these upregulation of pain-related nociceptors and channels; hence, BP should downregulate their activity by suppressing osteoclasts. Indeed, the effect of BP on the increased number of TRPV1 has not been clarified; however, BP should have an effect on TRPV1 because the receptor has been reported to modulate the synthesis and release of CGRP in sensory nerves. Furthermore, activation of these pain-related molecules induces increased production of c-Fos protein in the spinal dorsal horn, which is expressed by both noxious and non-noxious stimuli in the postsynaptic neurons of the spinal dorsal horn (Hunt et al., 1987). It is upregulated in response to various stimuli from the primary afferent neurons (Hunt et al., 1987; Menétrey et al., 1989; Morgan & Curran, 1991), thus it is used for a marker for neuronal excitation including pain. These findings such as increased production of pain-related channels, receptors, and proteins in DRG and activated spinal cord should be the another reason for osteoporotic pain.

Furthermore, BP is indicated to have a direct suppressive effect on pain-related sensory neurons. We demonstrated that risedronate inhibited axonal growth of neurite of pain-related small-sized DRG neurons isolated from rat neonates *in vitro* (Orita et al., 2010). The underlying mechanism remains unclear, but BP itself can produce an analgesic effect in osteoporotic patients by suppressing peripheral nerve function.

The analgesic effect of BP has come to be studied and recognized as reviewed here. Hence, BP can be a useful agent for dealing with osteoporotic pain.
When using BP, we have to be careful of its side effects such as gastroesophageal reflux disease in elderly patients with kyphosis, and jaw necrosis. However, BP should be of use after the exclusion of these possible side effects.

2.4 Hormone replacement treatment (HRT) and selective estrogen receptor modifier (SERM)

Estrogen deficiency is the most major pathology in osteoporosis. Thus there should be suggesting that hormone replacement treatment (HRT) could be an alternative treatment. However HRT is not recommended by several studies for its side effects: breast cancer, coronary heart disease, stroke, and pulmonary embolism (Rossouw et al., 2002). Regarding pain, several clinical reviews indicate that the low back pain treatment with HRT is not significantly effective (Symmons, et al., 1991) and not recommended (Gamble, 1995; South-Paul, 2001; Willhite, 1998).
Instead of HRT using estrogen, selective estrogen receptor modifier (SERM) has been used for the treatment and prevention of osteoporosis. Raloxifene is a benzothiophene-derivative SERM that binds to estrogen receptors α and β and exerts estrogen agonist effects or antagonist effects, depending on the target tissue: in bone tissue, raloxifene produces estrogen-like effects while it does not induce breast cancer(Cummings et al., 1999). Estrogen produces a suppressive effect on osteoclast activity by suppressing osteoclast differentiation and bone resorption (Luo et al., 2011). Hence, as an anti-osteoporosis agent, SERM increases BMD at the lumbar spine and hip region (Delmas et al., 1997), decreases bone turnover (Draper et al., 1996), reduces the risk of vertebral fractures in postmenopausal women with osteoporosis (Ettinger et al., 1999), and improves the lipid profile in healthy postmenopausal women (Walsh et al., 1998). Furthermore some possible mechanisms regarding the analgesic effect of raloxifene have been reported. First, it subserves the decreasing estrogen, which affects the sensitivity of nociceptive receptors (Hapidou & De Catanzaro, 1988) by facilitating pain production through pain-related neurotransmitters (Duval et al., 1996; Kawata et al., 1994). Second, pain modulation via central interactions using the endogenous opioids pathway system is reported (Quiñones-Jenab et al., 1997). By mimicking estrogen, raloxifene increases the number of glutamate receptors in the rostral cortex, nucleus accumbens, and striatum (Cyr et al., 2001), which are regions of the brain that have recently known to be involved in the nociceptive processing system (Chudler & Dong, 1995). Also, raloxifene affects dopamine receptors in the striatum and nucleus accumbens (Landry et al., 2002), which play an important role in nociception in acute and chronic pain conditions (Magnusson & Fisher, 2000). Furthermore, clinical studies suggested that raloxifene produces estrogen-like upregulating effects on plasma levels of β-endorphin (Florio et al., 2001), which acts as a neurotransmitter in the endogenous antinociceptive system. Hence, raloxifene affects nociceptive processing in CNS, possibly producing an analgesic effect. In addition, osteoclasts suppressed because of the estrogen-like effect of raloxifene should produce an analgesic condition through the reduced secretion of cytokines and reduce the risk of fractures.
While one study reported that raloxifene produced an analgesic effect in osteoporosis patients (Fujita et al., 2010), another study reported that the effect produced was not significant (Papadokostakis et al., 2006). This instability in estrogen or its alternative treatment should be due to the gradual decrease of estrogen receptor after menopause. And this shows that SERM should have some analgesic effect but might be better to be used in

combination with other osteoporosis treatment strategies to alleviate pain. Recently a new SERM, bazedoxifene, has been used in the clinical situation. Its analgesic effect is also should be investigated for osteoporotic pain patients.

2.5 Parathyroid hormone (PTH) and PTH analogue

Parathyroid hormone (PTH) stimulates bone formation by increasing the number of osteoblasts, partly by delaying osteoblast apoptosis (Jilka, 2007). Teriparatide, a recombinant of human PTH fragment 1-34 [rhPTH(1-34)], act as a bone anabolic agent which prevents, arrests, or partially reverses bone loss inducing new bone formation and improving bone microarchitecture (Peiqi Chen et al., 2007; Dempster, et al., 1993; Neer et al., 2001). The detailed mechanism of action of rhPTH is still under investigation, however the drug probably affects multiple pathways and alters the activity of osteoblasts, bone lining cells and osteocytes. Bone formation induced by PTH analogues not only increases BMD or bone mass but also improves the microarchitecture of the skeleton, thereby leading to improved bone strength and mechanical resistance (Kraenzlin & C. Meier, 2011). Hence, teriparatide has come to be used as one of the few anabolic agents for osteoporosis. A previous study reported that osteoporosis patients treated with teriparatide showed a greater analgesic effect on LBP than alendronate (Miller et al., 2005). Recently, a meta-analysis of five teriparatide trials showed that patients randomized to teriparatide had a reduced risk of new or worsening back pain during the active treatment phase compared with patients randomized to placebo or antiresorptive therapy (Nevitt et al., 2006).

Teriparatide can increase or decrease bone mass, depending on the mode of administration (Hock & Gera, 1992; Podbesek et al., 1983). Continuous infusions, which result in a persistent elevation of the serum parathyroid hormone concentration, lead to greater bone resorption than do daily injections, which cause only transient increases in the serum parathyroid hormone concentration(Tam et al., 1982). A previous study reported that a dose of 40 μg increased BMD to a greater extent than a dose of 20 μg but had similar effects on the risk of fracture and was more likely to produce side effects such as nausea and headache (Neer et al., 2001); this shows that physicians should be careful in prescribing the agent.

2.6 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are commonly used in clinical situations to reduce inflammation and pain. The mechanism of NSAIDs is mainly based on inhibition of cyclooxygenase (COX) enzymes, which convert arachidonic acid into prostaglandins (PG). In particular the COX-2 isoform is accepted as a proinflammatory enzyme that is induced by inflammatory stimuli and responsible for the generation of proinflammatory PGE_2 (Niederberger et al., 2008). PGE_2 induces proliferation and activation of osteoclasts via osteoblast activation, hence its inhibition can lead to inhibiting osteoclast formation, which lead to analgesic effect (Kaji et al., 1996). However, they are often ineffective on osteoporotic pain because osteoporotic pain involves multiple mechanisms described above. Hence, clinical physicians dealing with pain should consider the existence of osteoporotic pain when NSAIDs are barely able to produce an analgesic effect on patients complaining of chronic pain for several months. Such patients would be an osteoporosis patients with osteoporotic pain who have no evidence of injuries (Ohtori et al., 2010). Long-term administration of NSAIDs can produce some side effects such as gastric ulcers or renal function disorder; hence, physicians should be careful when prescribing NSAIDs to pain patients and should always try to target the origin of their pain.

3. Non-pharmacological treatment and osteoporotic pain

Non-pharmacological treatment strategies such as physical exercise, nutrition, diet, and following of certain habits are also used. These non-pharmacological approaches can improve BMD by preventing a fracture. Considerable evidence indicates that physical exercise can be most useful among these approaches. The major objective of physical exercise in the prevention or treatment of osteoporosis is to reduce the incidence of fractures. Additionally it has been reported that physical exercises produce an analgesic effect for osteoporotic pain besides bringing about improved physical function and vitality (Li et al., 2009). A basic study using OVX rats showed that physical exercise (5 days a week for 30 min on a treadmill for 30 days) led to a significant decrease in CGRP production when combined with risedronate; this combination suppressed CGRP production more than risedronate alone.Furthermore, this combination led to the maximum improvement in BMD (Fig. 3) (Orita et al., 2010). This is attributable to the activation of osteoblasts by both BP and physical exercise. BP is reported to increase total cellular protein, alkaline phosphatase activity, and type I collagen secretion in vitro (Iwamoto et al., 2005), and adequate mechanical stress is reported to activate osteoblasts (Ban et al., 2011); this is the reason why BP and exercise make an effective combination, which coincides with that of a previous report (Fuchs et al., 2007; Tamaki et al., Akamine et al., 1998). Other combinations of physical exercise and osteoporosis treatment strategies should be effective. However, another study reports that excessive physical exercise such as running for long periods has a negative effect on bone metabolism and proinflammatory status, and leads to increased osteoclast activity and elevated production of TNF-α and interferon-γ by CD8+ T cells (Sipos et al., 2008); further, excessive physical exercise can lead to fractures. Hence, the medical staff should suggest physical exercise programs suited to each patient.

4. Conclusion

Osteoporotic pain is a clinically-known condition, but investigation of its mechanism and origin has only been performed in recent years. Osteoporosis treatment predominantly aims to increase the BMD of patients in order to prevent possible fragile fractures that sometimes lead to a critical condition or result in a poor quality of life (QOL). Considerable evidence shows that using pharmacological or non-pharmacological treatment strategies for these patients not only improve their BMD but also relieve their pain. Physicians should always bear these matters in mind when choosing a treatment strategy that would best benefit patients with osteoporotic pain.

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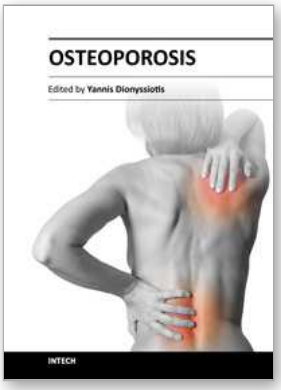

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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral 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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