Bisphosphonate Therapy for Osteoporosis

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Definition:

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, which predisposes the individual to an increased risk of fractures of the hip, spine, and other skeletal sites. [1] These fractures have devastating health consequences because of the associated increase in morbidity and mortality. Osteoporosis, a major public health problem, is becoming increasingly prevalent with the aging of the world population.

Prevalence of Osteoporosis:

In 2004, the US Surgeon General issued a warning, indicating that by 2020, half of all American citizens older than 50 will be at risk of fractures from osteoporosis and low bone mass if no immediate action is taken. [2] Ten million Americans over age 50 have osteoporosis, while 34 million have low bone mass or osteopenia and are therefore at risk for developing osteoporosis and its complication. Although older white women are clearly at risk, osteoporosis can strike anyone, at any age, including men, premenopausal women and ethnic minorities.

Osteoporosis is a leading underlying cause of fractures, especially in the elderly. An estimated 1.5 million people suffer a bone fracture related to osteoporosis each year. [3] Fractures are the most common musculoskeletal condition requiring hospitalization among Medicare enrollees (>one half million hospitalizations per year). Osteoporotic fractures also lead to over 800,000 emergency room encounters, more than 2.6 million physician office visits, and placement of nearly 300,000 individuals into nursing homes. [2] Hip fractures are the most devastating type of fracture, accounting for about 300,000 hospitalizations per year.

- About 20% of individuals with a hip fracture end up in a nursing home within a year.
- About 20% of senior citizens who suffer a hip fracture die within a year of fracture.
- The direct health care costs for osteoporotic fractures alone are up to 17 billion each year, and the number is expected to increase.

The clinical consequences and economic burden of this disease call for measures to assess individuals who are at high risk to allow for appropriate intervention.

Pathogenesis:

The development of osteoporosis is largely determined by changes in skeletal metabolism and architecture. Bone is a dynamic tissue that continuously remodels throughout life. This process allows the skeleton to increase in size during growth, respond to physical stress, and repair microdamage due to excessive or accumulated

stress or trauma. [4] The remodeling process is composed of a series of cellular events, which occurs on the surface of the bone, and is affected by both local and systemic factors. Osteoclasts, osteoblasts and osteocytes are the three major cells involved in bone remodeling. Osteoclasts, which are multinucleated cells formed by fusion of cells derived from hematopoietic stem cells, are responsible for resorbing bone. Osteoblasts, which are derived from mesenchymal precursors synthesize and secrete the organic matrix. Osteocytes are mature osteoblasts trapped within calcified bone, interconnected by long dendritic processes. They are believed to provide a communication network to transmit information about mechanical forces that can modify bone formation and bone resorption. The discrete sites of bone remodeling are called "bone remodeling units". At the beginning of the remodeling cycle, osteoclasts are recruited at the surface of the bone, and a group of osteoclasts excavates a resorption or erosion cavity. This phase is followed by filling in of erosion cavity with new bone by osteoblasts.

Normally, bone resorption and bone formation are tightly coupled, i.e., bone formation equals net bone resorption. The end result of this remodeling process is that the resorbed bone is replaced by an equal amount of new bone tissue and therefore, bone is neither gained nor lost. Thus, the mass of the skeleton remains constant after peak bone mass is achieved in adulthood. After age 30 to 45, however, the resorption and formation processes become imbalanced, with resorption exceeding formation. This imbalance may begin at different ages and varies at different skeletal sites and becomes exaggerated in women after menopause. The consequence of this imbalance is reduced bone mass, disordered skeletal architecture with development of microperforations and microfractures, hence increased risk of clinical fractures.

It is believed, based on available data, that high turnover can exert multiple adverse effects on bone, including acceleration of bone loss, disruption trabecular microarchitecture, increased mechanical stress concentration, and decreased mineralization density. [5] All of these changes could potentially reduce bone strength and resistance to fracture.

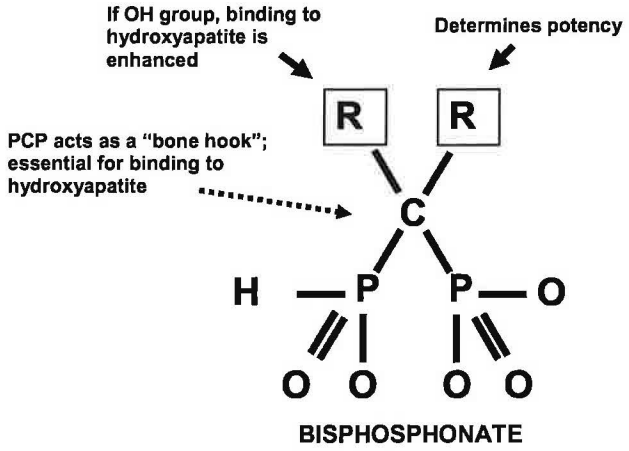


Figure 1. Structure of bisphosphonate

Mechanisms of action of bisphosphonates:

Bisphosphonates (BPs) are compounds composed of two phosphate molecules joined to a central carbon atom (P-C-P), Figure 1. They are analogs of pyrophosphate, containing an oxygen instead of a carbon atom. The bisphosphonates are produced from an identical P-C-P core, but differ structurally in the two side-chains, designated as R^1 and R^2. The phosphate ends of P-C-P avidly binds

with calcium hydroxyapatite, and anchors the bisphosphonates to the bone surface where they can be incorporated during remodeling. [6-8]

The side-chains attached to the central carbon atom distinguish the different members of the class from one another and determine the avidity of binding to the bone surface and the antiresorptive potency, The R^1 side chain determines the binding affinity of the compound. The R^2 side chain determines the anti-resorptive potency of the agent. Modifications in R^2 side chain, particularly the nitrogen-containing compounds, can result in a wide range of anti-resorptive activity. [6-8] BPs in the circulation are either rapidly absorbed onto the bone surfaces or excreted unmetabolized in the urine. It is believed that BPs taken up by the bone are exclusively localized under resorbing osteoclasts. However, there is evidence that they are more widely deposited, both in the active and inactive bone surfaces. [6] The activity of osteoclasts is rapidly inhibited by their by their uptake of BPs. Nitrogen-containing bisphosphonates (such as alendronate, risedronate, pamidronate, ibandronate and zoledronate) reduce osteoclast-mediated bone resorption by inhibiting farnestyl diphosphate synthase, an enzyme in the mevalonate pathway that is important in the maintenance of the cytoskeleton and cell survival. The presence of BP on the other bone surfaces provides a reservoir of the drug, which, over the coming months and years could affect the future generations of osteoclasts that attempt to resorb these surfaces. It is also likely that there is local reuptake of BPs released from bone. As new bone is formed, previously deposited BPs become buried and are unable to affect bone turnover. They can, however potentially be available years later. It is possible that progressive labeling of the entire skeleton could occur with long-term treatment with BPs.

Non-nitrogen containing BPs (such as etidronate and clodronate) inhibit bone resorption by producing toxic analogs of ATP that cause premature death of osteoclasts. BPs have two fundamental biological effects: a) inhibition of calcification when given at high doses and b) inhibition of bone resorption. [6]

Bisphosphonates in the treatment of osteoporosis:

BPs are considered the most potent anti-resorptive agents currently available for the treatment of osteoporosis, and have been shown to have a greater effect on bone density compared to the other anti-resorptive agents (6-10% vs. 1.5-2%). [9-11] In addition, administration of BPs results in a more marked reduction in the biochemical markers of bone turnover. [10-12] At the tissue level, osteoid thickness, osteoid volume and surface were all significantly reduced during alendronate therapy. Alendronate has been shown to significantly reduce mineralizing surface and activation frequency (92% and 96% at 2 and 3 years of treatment, respectively). [13] Administration of risedronate results in a 47% decrease in activation frequency after 3 years of treatment. [14]

Several placebo-controlled trials have shown that these agents decrease bone turnover, prevent progression of bone loss, increase bone mineral density and decrease the risk of fractures. [9-33]

Alendronate (Fosamax®), a nitrogen-containing BP was approved by the FDA in 1995 and was the first BP for the treatment of osteoporosis. A study of over 500 postmenopausal women with osteoporosis showed that administration of alendronate increased the bone mineral density (BMD) at the spine and hip: 10 mg/day increases the spine BMD by 9% and femoral neck by 6% over 3 years treatment period compared to placebo-treated individuals. [15] BMD and bone turnover marker changes seen with 10 mg/day are similar to those seen with 70 mg/week. [16] Based on these results, the weekly dose was approved in 2000.

The Vertebral Fracture arm of the Fracture intervention trial (FIT), which is a study of over 2000 women with prevalent vertebral fractures showed a significant reduction in the incident vertebral fracture by 47% in the alendronate-treated individuals compared with placebo. In addition, wrist and hip fractures in the alendronate-treated patients were also lower (48% and 51% for wrist and hip fractures, respectively) compared to placebo. [17] Several studies have suggested reduction in fractures within 1 year of alendronate treatment. [18,19] Moreover, alendronate therapy has been shown to reduce days of reduced activity, days in bed and use of hospital services. [20]

In men, BMD increases during alendronate treatment were similar to those in women, with a trend towards lower vertebral fractures. [21] A study which involved 477 men and women receiving glucocorticoid therapy, alendronate significantly improved spine and hip BMD over a 48 week period. [22]

For the treatment of postmenopausal osteoporosis, the recommended dose is 10 mg/day or 70 mg/week. For prevention, the recommended dose is 5 mg/day or 35 mg/week. For glucocorticoid-induced osteoporosis, the indicated dose is 5 mg/day for men and estrogen-replete women or 10 mg per day for postmenopausal women who are not taking estrogen.

Risedronate (Actonel®) Administration of risedronate over a 3-year period increases spine BMD by 4-5% and hip BMD by about 2-4 % compared to placebo, and reduces bone turnover markers by 40-60%. [23] A weekly dose was shown to have a similar effect on BMD and bone turnover markers and was approved by the FDA in 2003. [24]

Risedronate, at a dose of 5 mg/day reduced vertebral fractures by 40-50% in 2 3-year studies that involved about 3600 women with prevalent fractures. [23,25] The reduction was evident as early as 1 year of treatment. Osteoporotic nonvertebral fractures were decreased by 39%. [23] The HIP Intervention Program Risedronate (2.5 and 5 mg risedronate per day versus placebo), which enrolled over 9000 women over 70 years of age at high risk of hip fractures showed a 30% overall reduction in hip fractures in the treated group compared to placebo. [26] In a subset of women between ages 70-79 years with very low bone density (T-scores of < -3 or -4), a 40% reduction in fractures was observed compared to placebo.

Risedronate has been shown to prevent bone loss in early postmenopausal women, [27] prevent glucocorticoid-induced bone loss in patients starting glucocorticoid therapy [28] and to increase BMD in patients who have been on glucocorticoid therapy for about 5 years. [29] Risedronate is approved for the treatment of postmenopausal, male and glucocorticoid-induced osteoporosis.

Ibandronate (Boniva®) given as a daily dose of 2.5 mg was shown to increase spinal BMD by 5% and hip BMD by 3-4% over 3 years. [30] In addition, treatment with ibandronate resulted in 46-60% reduction in bone turnover markers. [31] A 50% reduction in new vertebral fractures has been shown in women with prevalent vertebral fractures treated with 2.5 mg/day over 3 years. [30] No significant reduction in nonvertebral fractures was noted, although a post hoc analysis showed a 69% reduction in nonvertebral fractures in patients with femoral neck BMD T-score of < -3 (approximately 15% of the study population).

A trial comparing 2.5 mg/day to 100 and 150 mg once a month showed similar or better BMD gains for the monthly formulation. [32] The once a month formulation was approved by the FDA in 2005.

Zoledronic Acid (Reclast®) has not been approved by the FDA for the treatment of osteoporosis, but a double-blind, placebo-controlled trial involving postmenopausal women with osteoporosis randomly assigned to receive a single 15-minute infusion of either zoledronic acid (5 mg) or placebo yearly for 3 years showed a 70% reduction in the risk of morphometric vertebral fracture during a 3-year period, as compared with placebo (3.3% in the zoledronic acid group vs. 10.9% in the placebo group) and a 41% reduction in the risk of hip fracture (1.4% in the zoledronic acid group vs. 2.5% in the placebo group). Nonvertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively ($P<0.001$ for all comparisons). Zoledronic acid was also associated with a significant improvement in bone mineral density (6.71%, 6.02% and 5.06% for the lumbar spine, total hip and femoral neck, respectively) and >50% reduction in bone turnover markers. [33]

The mechanisms by which therapy with anti-resorptive agents can decrease fractures are probably multifactorial. First, the slower rate of bone remodeling allows the newly formed bone to be laid down and fill the resorption cavities, therefore, partially correcting the imbalance between bone resorption and bone formation. [34] Second, reduced bone turnover rate allows for primary and secondary mineralization to take place which results in an increase in the degree of mineralization of newly formed bone. [35,36] Higher degree of mineralization increases bone density and the bone's ability to resist fracture. Lastly, administration of anti-resorptive agents, especially bisphosphonates results in the reduction of the size of remodeling space, which could prevent thinning and perforation of trabecular plates. [34] All these factors are believed to be responsible for the increase in BMD as measured by DXA and decrease in fracture rates during therapy with anti-resorptive agents.

The unique effects of BPs have made them the most potent [11] and the most used [37] class of anti-resorbing agents available, accounting for 73% of the total prescriptions for osteoporosis treatment written in 2003.

Safety Concerns with Chronic Therapy:

Cases:

Case 1: 68-year-old lady who was referred for further evaluation and management of osteoporosis. She developed natural menopause at age 52 and was placed on hormone replacement therapy. In 1997, she had a screening bone density which showed osteoporosis at the femoral neck and total hip. She has no history of atraumatic fractures at that time. She was already taking calcium with D and Premphase (>12 years) and Fosamax was added. A repeat bone density in 1999 showed improvement and medications were continued. In March 2001, she developed pain in the pelvic area, was found to have fracture of the sacrum. This was not associated with trauma. Fracture apparently healed after 8 weeks. In July 2001, she developed pain in the groin area and was found to have fracture of the ischium. She was seen by her physician and was prescribed Miacalcin in addition to the estrogen, calcium and Fosamax. Repeat X-ray 2 months after the fracture showed no evidence of fracture healing (Figure 2).

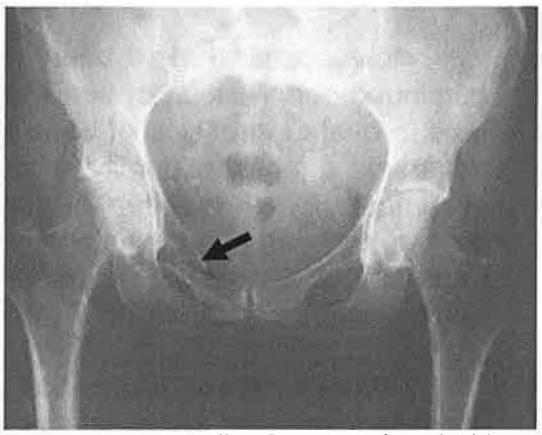


Figure 2. Non healing fracture of the ischium

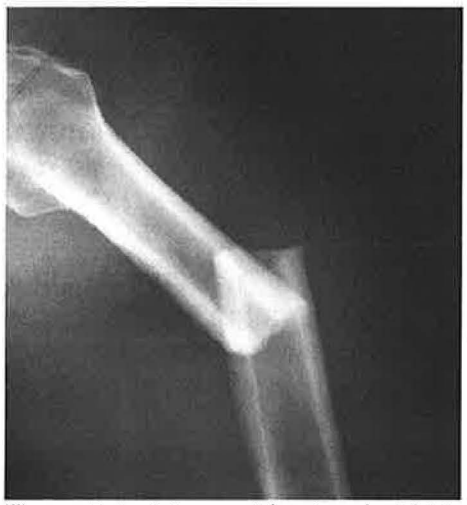


Figure 3. Left femoral fracture in 2003

Case 2: 68 year old white male who presented with metatarsal stress fractures at the age 60 years. BMD at the time (1997) showed only osteopenia in the femoral neck, and normal spine BMD. He was started on Alendronate 10 mg/d, which was later switched to 70 mg/week. BMD in 2002 showed an increase in spine BMD over 5 years of therapy. In Jan 2003 he stepped off a step in his garage and sustained a fracture of the left femoral shaft, Figure 3. He underwent open reduction and internal fixation (ORIF), and recovery was uneventful.

He was well until January 2004, when while walking down a corridor he felt a snap in the middle of the right thigh and fell. X-ray showed fracture of the right femoral shaft, figure 4 requiring ORIF.

Work-up showed normal serum chemistries, kidney and liver function, PTH and 25-hydroxyvitamin D, Bone histomorphometry showed severely suppressed bone resorption and formation parameters, hence the term "severe suppression of bone turnover". [38]

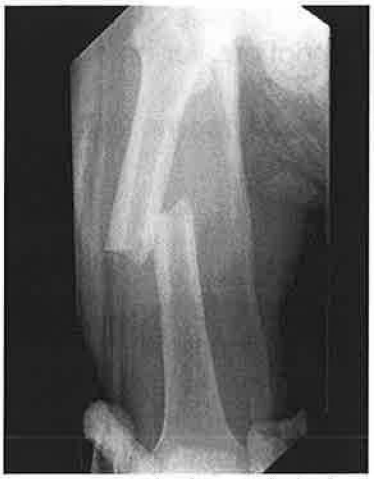


Figure 4. Right femoral shaft fracture in 2004.

a. Severe Suppression of bone turnover (SSBT):

Questions have been raised on whether continued suppression of bone turnover by BPs could lead to oversuppression of bone turnover, which could adversely affect the quality of bone. Bone quality is influenced by a number of factors, which include morphology and architecture, [39-42] rate of bone turnover, [43] degree of mineralization [44,45] and microdamage accumulation [46] and the last three factors are closely interrelated.

Bone turnover allows the skeleton to respond to physical stress and to repair microdamage due to excessive or accumulated trauma. Therefore, excessive and prolonged suppression could potentially adversely affect the quality of bone and impair fracture healing. The role played by suppressed bone turnover in the loss of skeletal strength was first appreciated in the 1900s when Albers-Schonberg described autosomal dominant osteopetrosis, a condition characterized by high bone density, defective bone resorption and fractures with minimal trauma. [47] The concept that reduced bone turnover may lead to fractures was further supported by reports of insufficiency fractures of the femoral neck, sacrum and pelvis in osteoporotic patients. [48] It is believed that these fractures occur in weakened bone that cannot withstand repetitive mechanical loading. It was Harold Frost who first observed microdamage in bone, and proposed that low bone turnover could impair the bone's ability to repair strain-related microdamage, and could lead to accumulation of microcracks or microdamage. [49] Several animal and postmortem human studies have shown that microdamage in bone reduces the elastic modulus of the tissue. [50-56] Norman et al. showed that fracture toughness of the femoral shaft decreases significantly with increasing microcrack density. [57]

Animal studies have linked bisphosphonate therapy with the accumulation of microcracks. Mashiba and colleagues showed that administration of high-dose aminobisphosphonates to female beagles for 12 months increased accumulation and length of rib microcracks, proportional to the reduction of activation frequency. [58] Following pharmaceutical suppression of bone remodeling, there was a 2- to 7-fold increase in microdamage accumulation, which was associated with a 20% reduction in the bone's ability to sustain deformation without breaking. [58-59] How these biomechanical measurements translate to clinical outcome is yet to be established.

Chronic suppression of bone turnover by bisphoshates will allow more time for secondary mineralization to continue. [36] This could result in "hypermineralized" and more homogeneous bone. The degree of mineralization strongly affects the mechanical and material properties of bone, with low mineralization levels (as seen in osteomalacia) causing reduced stiffness and strength, and hypermineralization likely contributing to reduced fracture toughness. [45] Moreover, more homogeneous tissue offers less obstruction to crack propagation and extension. [60] The slower rate of bone turnover during bisphosphonate therapy is associated with increased tissue mineral content. After 2 and 3 years of alendronate therapy, the degree of mineralization in the cortical and trabecular bone showed a clear shift toward the highest mineralization values. [36] While higher mineral content makes bone tougher and more resistant to fracture, highly mineralized and more homogeneous bone is more brittle.

In 2005, our group described 9 patients who sustained spontaneous non-spinal fractures while on alendronate therapy, six of whom displayed either delayed or absent fracture healing for 3 months-2 years during therapy. [38] Four out of nine were on alendronate for 6-8 years, 3 were on both estrogen and alendronate and 2 were also on long-term glucocorticoids. Histomorphometric analysis of the cancellous bone showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. Osteoclastic surface was low or low normal in 8 patients and eroded surface was decreased in 4. Matrix synthesis was markedly diminished with absence of double-tetracycline label and absent or reduced single-tetracycline label in all patients. Our findings suggest that severe suppression of bone turnover (SSBT) can potentially develop during long-term alendronate therapy, which could in turn result in increased susceptibility to, and delayed healing of non-spinal fractures. This report was criticized for being an uncontrolled trial. In addition, it was argued that glucocorticoid or estrogen therapy (in some of the patients) could have lead to the over suppression of bone turnover when bisphosphonate was added.

Schneider, in 2006, described a case of a previously healthy postmenopausal woman, who experienced two non-traumatic stress fractures (femur and metatarsal bone) while on combination estrogen and alendronate therapy. [61] Nonunion of the femoral fracture was noted after 9 months despite intramedullary rodding and external electrical stimulator. Revision intramedullary procedure was later performed but to no avail. Fracture healing was observed only when alendronate was discontinued. The medication was re-started after 2 years because of a decline in bone density. However, one year later, she developed moderate pain in her right foot and was diagnosed to have stress fracture of the second metatarsal bone. Alendronate was again discontinued, and the fracture healed after several months.

Armamento-Villalreal, et al. [62] described a 35-year-old man who was referred to their clinic in 1996 because of wrist and pelvic fractures after mild trauma. The z-scores for bone mineral density (BMD) on dual-energy x-ray absorptiometry were -4.9 at the spine and -1.7 at the femoral neck. Histomorphometric analysis of bone biopsy sample was consistent with high-turnover osteoporosis. Work-up for secondary causes of osteoporosis were negative. The patient was started on 10 mg of alendronate daily and

1000 mg of calcium daily. After 5 years of treatment, he developed new thoracic vertebral compression fractures, despite improvement in his serial BMD measurements (with z-scores of -2.9 at the spine and -0.8 at the femoral neck). The patient discontinued alendronate on his own after 6 years of treatment. One year later, he developed a subtrochanteric fracture of the right femur after mild trauma. A bone biopsy showed severely decreased trabecular connectivity, with many small islands of bone, decreased marrow cellularity, a lack of osteoid on trabecular surfaces, and an absence of tetracycline labeling, which suggest marked suppression of bone turnover. The patient also displayed delayed fracture healing, similar to the patients described by our group in 2005.

Goh, et al. [63] recently reported 13 women, 9 of whom were on alendronate, who presented with subtrochanteric fracture after minimal trauma. Patients who were on alendronate were younger compared to those who were not. They were on alendronate for 2.5-5 years. Five out of nine in the alendronate-treated group experienced prodromal pain in the affected hip 2-6 months prior to the development of fracture. The fractures were mainly at the metaphyseal-diaphyseal junction. An interesting observation by authors is that fractures occur in patients with radiologically good cortical bone stock. In addition, they noticed thickening in the lateral femoral cortex in 6 of the alendronate-treated patients, and in three, the cortical thickening was bilateral. The authors suggested that prolonged suppression of bone remodeling may be associated with a new form of insufficiency fracture of the femur.

Although there were no histomorphometric confirmation of severe suppression of bone turnover in the cases reported by Schneider and Goh et al., the history of atraumatic or low trauma fractures occurring at sites that are not usually affected in osteoporosis are consistent with our initial description of the clinical presentation of severe suppression of bone turnover.

Since the original report [38], we have observed 10 additional cases with the same clinical presentation. The patients were given BPs for either postmenopausal osteoporosis/osteopenia or glucocorticoid-induced osteoporosis. Majority of the patients (8 of 10) were on combination therapy with BPs and either estrogen or selective estrogen receptor modulator (SERM) for 3-10 years and 9 of the 10 displayed delayed fracture healing (6 months to 4 years). Bone histomorphometry in 5 of the 7 patients who had bone biopsy showed SSBT. Two patients had low bone formation, one of whom underwent bone biopsy 9 months after discontinuation of BP. Based on our experience and those of others, a number of factors appear to increase the risk of developing SSBT, Table 1.

Table 1. Potential Risk Factors for SSBT:

1. Duration of therapy (usually > 5 years)
2. Combination therapy with estrogen and/or other anti-resorptive agents.
3. Concomitant glucocorticoid therapy.
4. Low pretreatment bone turnover

Earlier Clues:

There have been clues from previously published studies which suggest that long term therapy with bisphosphonates and too much suppression of bone turnover may have a negative effect on the bone. Ott was first to suggest that chronic treatment with alendronate might impair the mechanical strength of the bone, noting the apparent increase in fracture rate with prolonged therapy. [64,65] This was challenged by the authors of that report; they pointed out that the study was not adequately powered to evaluate meaningful fracture risk reduction. [66] A study on postmenopausal women maintained on estrogen showed that the addition of bisphosphonate resulted in further reduction in bone turnover. [67] The spinal fracture rate however, appeared higher in the combined estrogen-bisphosphonate group, compared with the group on bisphosphonate alone, although the difference was not statistically significant. In 2002, Whyte el al. reported a case of bisphosphonate-induced osteopetrosis in a 12-year-old boy who presented with high bone density and increased susceptibility to spontaneous fractures. [68] However, the dose of bisphosphonate given to this patient was 4 times the usual dose given in children with osteogenesis imperfecta. Lastly, Bauer et al. showed that alendronate therapy was not as effective in reducing non-spinal fractures in osteoporotic women with low baseline bone turnover compared to those in the highest tertile of pretreatment bone turnover markers. [69] Moreover, the incidence of nonspinal fractures tended to be higher in non-osteoporotic women with low bone turnover prior to treatment. These findings suggest that in patients with low bone turnover prior to initiation of therapy, further suppression might increase the risk of non-spinal fracture(s) and that bisphosphonates may not be the best treatment option for this group of patients.

b. Effect of fracture healing:

Concerns have also been raised on the effect of chronic bisphosphonate therapy on fracture healing. By suppressing bone turnover, one might expect that bisphosphonate could delay fracture healing. Previously published reports however, have been conflicting. [70-74] A study on a beagle dog model suggested that treatment with ibandronate did not adversely affect bone healing. [70] On the other hand other studies have suggested otherwise. Studies on the effect of etidronate, clodronate, incandronate and alendronate have shown an increase in callous formation but

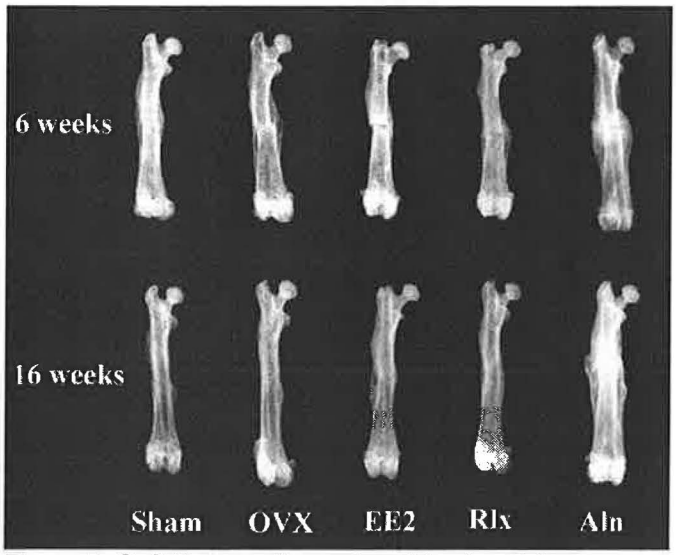


Figure 5. Soft X-ray radiographs of fractured femora. External callus formation was visible in all femora at 6 weeks. Fracture lines disappeared in OVX at 16 weeks, 56% fracture lines were still visible in ALN at 16 weeks.

delayed callous remodeling. [71-74] Cao et al. compared the effect of ovariectomy, sham operation, alendronate, estrogen and raloxifene on fracture repair and found that ovariectomy-stimulated bone turnover resulted in the fastest progression of fracture repair that was most delayed with alendronate treatment. [74] Alendronate strongly suppressed remodeling of the callus, resulting in highest content of woven bone, persistent visibility of the original fracture line and lowest content of lamellar bone compared with the other groups 16 weeks after the fracture. Estrogen and raloxifene had effects that were similar to sham. Therefore, while estrogen and raloxifene had an insignificant effect on the progression of fracture repair, alendronate treatment caused marked suppression of bone resorption and formation activity, and negatively affected fracture healing. Data on the effect of bisphosphonates on fracture healing in humans are limited. In children with osteogenesis imperfecta, administration of either pamidronate or alendronate does not appear to interfere with fracture healing. [75] However, delayed mineralization of osteotomy sites has been observed prompting some surgeons to discontinue pamidronate therapy six months before an elective procedure and until after callus formation is noted. [76] Six out of nine patients in our report on SSBT displayed delayed fracture healing. [38]

b. Osteonecrosis to the jaw (ONJ):

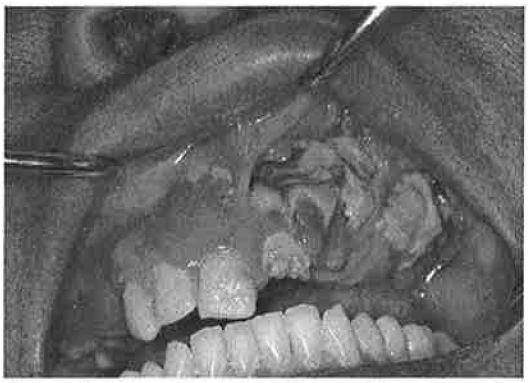


Figure 6. Exposed necrotic maxillary bone in a patient receiving zoledronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. [81]

Since 2003, several case reports have documented a newly appreciated oral complication of bisphosphonate therapy: osteonecrosis of the jaw, requiring surgical removal of affected tissue has been reported in patients who had received intravenous bisphosphonate for malignancy and in some patients who took oral bisphosphonate for osteoporosis. [77-84] It usually presents as an area of exposed, necrotic bone in either the mandible or maxilla, which persists for several months. On December 14, 2006, the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis convened in Geneva to review the available data and published guidelines in this rare but serious condition. [78] The following definition of ONJ was endorsed by the group "*Exposed bone in the mandible or maxilla or both that persists for at least 8 weeks, in the absence of previous radiation or of metastases in the jaws*". As of 2006, the total number of reported cases of possible ONJ in people taking alendronate is approximately 170 worldwide, according to Merck and Company (Whitehouse Station, NJ); approximately 12 people taking Actonel according to Procter and Gamble Pharmaceuticals (Cincinnati, OH); and one person taking ibandronate (Roche Pharmaceuticals, Basel, Switzerland). [82] In cancer patients being treated with intravenous BPs to reduce the number of skeletal events and treat hypercalcemia, the

reported rate is 95 per 100,000 patient treatment years. It is commonly seen in patients with metastatic breast cancer or multiple myeloma. [78]

The underlying mechanisms for the development of ONJ are yet to be elucidated. One hypothesis is that ONJ may be related to sustained and excessive inhibition of bone turnover and accumulation of microfractures. Others suggest the role of decreased angiogenesis leading to bone cell necrosis and apoptosis. [82]

The typical clinical presentation of ONJ includes pain, soft tissue swelling, loosening of the teeth, drainage and exposed bone. [79-82] Symptoms may occur simultaneously in the bone or more commonly, at the site of a previous dental extraction. ONJ may also remain asymptomatic for weeks and months and may become evident only after the finding of exposed bone in the jaw is discovered on routine examination.

Risk factors for the development of ONJ in osteoporotic patients receiving BP therapy have not been systematically investigated because of the low incidence. A recent study in cancer patients suggest that higher dose of BPs, longer duration of treatment, dental extraction and periodontitis are associated with increased risk of developing ONJ. Presence of co-morbid diseases such as rheumatoid arthritis, diabetes, treatment with immunosuppressive drugs or chemotherapy also appears to increase the risk for ONJ. [78,82,83]

General Management of ONJ:

In BP-treated osteoporotic patients, no specific interventions prior to starting BP therapy are required except to encourage routine dental care. If a BP-treated patient requires maxillofacial surgery and risk factors such as diabetes and glucocorticoid therapy are present, close follow-up is recommended. Use of antibiotics and mouth rinses should be considered. Treatment of ONJ is empirical. To date, no treatment has been established, although several recommendations have been published. [78,82-84]

Future Directions:

Nobody can deny that BPs have had a major impact in the management of osteoporosis. They have been proven to be effective in preventing bone loss, improve bone density and decrease fractures in osteoporotic individual. However, it should be emphasized that these agents have a very long skeletal half-life. Additional studies are therefore needed to address at least two important issues: First is, the safe optimal duration of therapy with BPs, and second, whether other treatment strategies incorporating the beneficial effects of BPs could reduce the risk of skeletal adverse effects.

Significant fracture protection has been shown after 4 years of treatment with alendronate and 5 years after risedronate. [18,85] A recent study [87] suggests that the anti-fracture efficacy of alendronate is durable for up to 5 years after discontinuing the

drug. Therefore, it seems reasonable to consider a "drug holiday" after 5 years of BP therapy, unless the patient still remains at high risk for fractures.

Others have proposed intermittent teriparatide (PTH) therapy for patients previously treated with BP for 5 years or more and who remain at high risk for fractures. [87] A study comparing the effect of PTH on BMD and bone turnover in women treated with either alendronate or raloxifene for 18-36 months showed that BMD and bone turnover increased after PTH in both groups. [88] Raloxifene therapy in patients previously treated with alendronate prevented spinal bone loss compared to placebo. [89] Similarly, the increase in bone turnover markers after stopping alendronate was less pronounced in the raloxifene group. Thus, switching to a non-BP anti-resorptive agent presents a viable option.

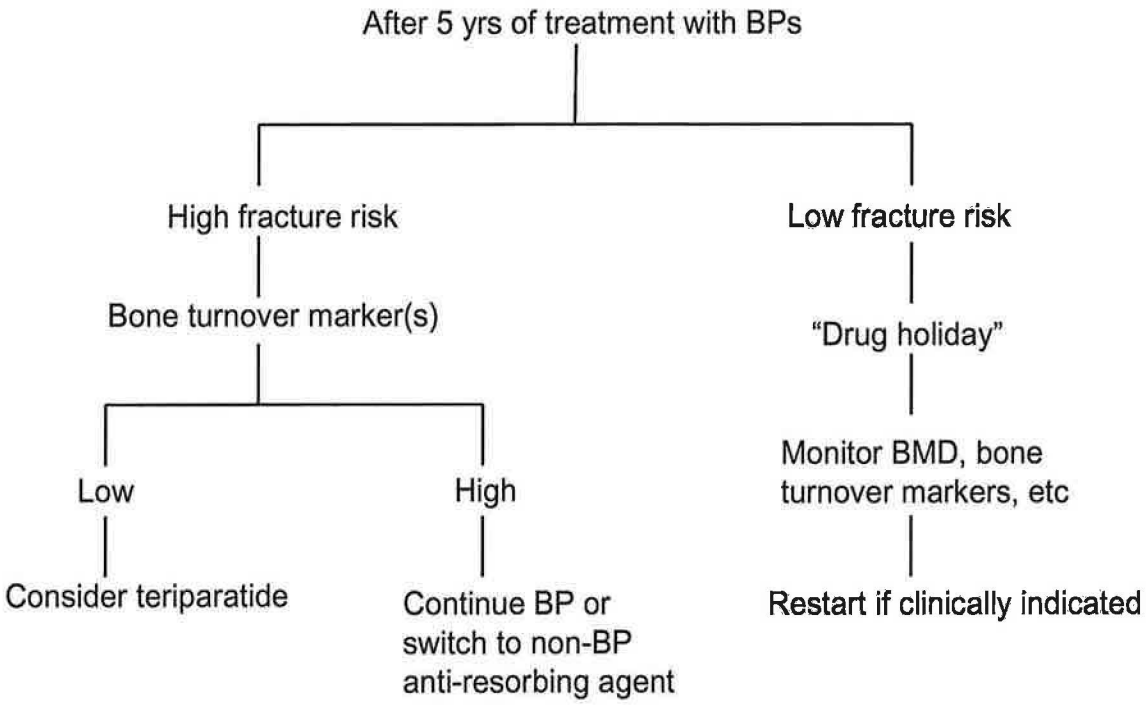
More studies are clearly needed to understand the pathogenesis of and identify this problem before it (especially fracture) occurs. In the meantime, we should put emphasis on awareness of the potential adverse effects of these agents. A few potential risk factors have been identified based on our experience (Table 1), but no causal relationship has been established.

Summary:

Although rare, there is increasing evidence which suggests that chronic BP therapy could lead to significant skeletal adverse events such as SSBT and osteonecrosis of the jaw. At present, it is not known how many patients are at risk of developing SSBT and ONJ nor do we know their pathogenesis. Given the large number of patients exposed to BPs, even a small fraction of exposed patients could be clinically relevant. Further studies to elucidate the pathophysiology of these clinical entities are certainly warranted. A better understanding of its mechanism will help formulate ways to either prevent or reverse these complications. In the meantime, prudent clinical judgment based on available data is reasonable.

A suggested algorithm based on available data is depicted in the Figure 7; after 5 years of therapy, consider a "drug holiday" for most patients. These patients should be monitored (BMD, bone turnover markers, fractures, etc) and therapy should be re-instituted if there are clinical indications such as decline in BMD or rise in bone turnover markers. For patients with very low BMD and high fracture risk, one may consider switching to PTH or a non-BP anti-resorptive agent.

Figure 7: Suggested algorithm to prevent SSBT



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