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REVIEW ARTICLE

Bisphosphonates in Orthopedics: Evidence-based Review of Indications and Adverse Effects

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ABSTRACT

Bisphosphonates (BPs) are clinically the most important class of antiresorptive agents available to treat diseases characterized by osteoclast-mediated bone resorption. These agents have a potent effect on the skeleton and are in common use for treatment of osteoporosis, Paget's disease, and metastatic bone disease in adults as well as in the treatment of pediatric disorders, such as osteogenesis imperfecta, Perthes' disease, and fibrous dysplasia. Although initial investigations had demonstrated an acceptable safety profile of bisphosphonate drugs, but recently this has been questioned by some authors. In this article, we review the chemistry, pharmacokinetics, and pharmacodynamics of these agents in brief and the orthopedic applications as well as adverse effects in detail.

Keywords: Adverse effects, Bisphosphonates, Indications, Review.

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INTRODUCTION

Bisphosphonates (BPs) are synthetic, pyrophosphate analogs containing two phosphonate groups attached to a central carbon atom that replaces the oxygen in pyrophosphate (the P-O-P bond has been replaced with a nonhydrolysable P-C-P bond (Fig. 1).[1] They are metabolically stable analogs of inorganic pyrophosphate and have a strong affinity for bone, especially areas of high turnover.

The BPs can be grouped into three generations according to their side chains:

1. First-generation BPs contain minimally modified side chains (e.g., medronate, clodronate, and etidronate) or a chlorophenyl group (e.g., tiludronate).

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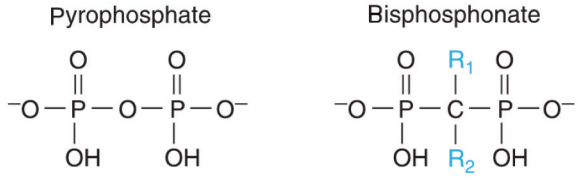

Fig. 1: Molecular structure of the bisphosphonates and the position of side chains

2. Second-generation BPs or amino-BPs contain an N-atom in the side chain (e.g., Pamidronate, Alendronate, and Ibandronate). These are 10 to 100 times more potent than the first-generation drugs.
3. Third-generation BPs contain an N-atom within a heterocyclic ring (e.g., Risedronate and Zoledronate). These are up to 10,000 times more potent than the first-generation drugs.

MECHANISM OF ACTION OF BPs

Bisphosphonates are antiresorptive agents; they inhibit bone resorption by acting directly on osteoclasts. They reduce the rate of excessive turnover and slow or arrest the progressive deterioration of micro-architecture and loss of bone tissue, and may in fact partially reverse these changes.[2] Bisphosphonates act preferentially over the active bone remodeling sites on the bones by binding to exposed bone minerals, thus rapidly and specifically inhibiting bone resorption mediated by osteoclasts in a dose-dependent manner.[3,4] This improves the existing bone micro-architecture and mineralization and slows or prevents the progressive loss of structural elements.[5] Continuous (daily or weekly) treatment with nitrogen-containing BPs causes a rapid and sustained improvement in bone micro-architecture, together with an increase in bone mass, leading to improved mechanical strength and reduced fracture risk.[6] Newer nitrogen-containing BPs also inhibit components of the intracellular mevalonate pathway of cholesterol biosynthesis and protein prenylation thus affecting GTPase formation.[7,8] The latter causes disruption of integrin signaling, altered membrane-protein trafficking, loss of membrane ruffling, cytoskeleton disruption, and induction of apoptosis of osteoclasts.[9]

Binding affinity and antiresorptive potency differ among the compounds. The side chains (Fig. 1) influence the binding affinity (R1 side chain) and the antiresorptive

potency (R2 side chain).[10] Both oral and parental preparations are available for clinical use. Only about 1% of an orally administered dose is absorbed in ideal conditions and taking a BPs with food or anything containing divalent cations will completely block its absorption. They are not metabolized systemically and the half-life in plasma is short. Half of the absorbed dose binds to bone surfaces, most avidly at the sites of active remodeling and the rest is excreted rapidly by kidneys. The skeletal capacity is large and the binding sites are virtually unsaturable.[11] In the acidic environment with enzymes beneath an active osteoclast, BPs are released from the bone and enter the osteoclasts. This causes loss of resorptive function and accelerates apoptosis of these cells, thus reducing the osteoclast-mediated bone resorption and bone turnover. Maximum effect is noted in 3–6 months and with continued treatment and is maintained in a steady state for 10 years or more.[12,13]

CLINICAL USES OF BPs IN ORTHOPEDICS

Till date, eight BPs have been approved for clinical use by US-Food and Drugs Administration (FDA). These are pamindronate, clodronate, etidronate, tiludronate, alendronate, ibandronate, risedronate, and zolindronic acid.[14] Last four are freely available in India. The primary indication is to increase the bone mass and reduce the fracture risk in patients with osteoporosis. Other common indications are Paget's disease and bone metastases. They are also useful in lowering the elevated levels of blood calcium in patients with cancer (multiple myeloma, hypercalcemia of malignancy). Other indications and contraindications for their use are listed in Table 1.

Table 1: Clinical uses of BPs

Adult bone diseases
1. Osteoporosis
2. Solid tumors and metastatic bone disease
3. Hypercalcemia of malignancy
4. Paget's disease
5. Avascular necrosis (AVN)
6. Primary bone-marrow edema syndrome
7. Stress fractures
8. Arthroplasty
9. Reflex sympathetic dystrophy (CRPS-1)

Pediatric bone diseases
1. Fibrous dysplasia
2. Osteogenesis imperfecta
3. Perthe's disease

Contraindications
1. Pregnancy and women who are actively planning conception
2. Chronic kidney disease
3. Osteomalacia and patients with low serum calcium or vitamin D levels
4. Heart diseases like heart failure, coronary artery disease and arrhythmias
5. Diabetes mellitus
6. Oral formulations are practically contraindicated in patients with esophageal disease or patients on strict bed rest who cannot stay upright for an hour

Osteoporosis

Use of BPs for treatment of osteoporosis is now well-established [15]. They can be used in postmenopausal osteoporosis as well as in idiopathic osteoporosis in men, in glucocorticoid-induced osteoporosis, and in secondary osteoporosis with various diseases and drugs.[16-18] Weekly and monthly oral formulations are available for prevention and treatment. Intravenous (IV) formulation can be used in patients with low gastrointestinal (GI) tolerance and noncompliant patients. Black et al[19] found a significant reduction in vertebral fracture risk (70%) and vertebral fractures (40%) with use of an annual infusion of 5 mg zolendronic acid over a period of 3 years. Bisphosphonates also reduced the mortality rate following hip fractures by 28% over 3 years.[20] Similar data are also presented by Kanis et al.[15]

This is a common belief that BPs therapy should not be continued beyond 3 to 5 years. Many studies claim that BPs given over a period of 2–3 years will cause brittle bones.[21,22] But the same has not been proven in larger longitudinal studies.[11-13] Current studies are unable to support the earlier concept of basic conversion of the bone into "frozen bone" with administration of BPs and have proven rising bone density (about 1% or more annually) even 10 years after BPs treatment.[12] The differentiation of bone turnover in osteoporosis as "high turnover" and "low turnover" is currently not relevant to the choice of BPs. After discontinuation of BP therapy, fracture reduction can be expected with positive after-effects of several years.

Watts and Diab[11] in his review on long-term use of BPs in osteoporosis recommends a drug holiday after 5 to 10 years of BP treatment. The duration of treatment and length of the holiday are based on fracture risk and pharmacokinetics of the BP used. Patients at mild risk might stop treatment after 5 years and remain off as long as the bone mineral density is stable and no fractures occur. Higher risk patients should be treated for 10 years, with a holiday of no more than a year or two. He also recommended non-BP treatment for osteoporosis during this holiday period.

Antitumor Activity—Solid Tumors and Metastasis

Bone metastasis is probably the most symptomatic metastatic disease. It has a tremendous impact on the quality of life, mobility, and independence. Bone metastases eventually develop in > 80% of patients with

breast, prostate, or kidney malignancies. This may present as hypercalcemia, bone pain, pathologic fracture, and spinal cord compression. The invasion of malignant cells into the bone microenvironment causes a breakdown in the normal, tightly controlled bone-remodeling process, leading to an uncoupling of cellular function and an excess of osteoclastic over osteoblastic activity. This disruption of bone homeostasis leads to osteolysis, skeletal destruction, and a risk of pathologic fractures.[23]

There is a growing body of evidence that BPs possess direct antitumor activity against a variety of cancers as well as act synergistically when combined with other anticancer agents.[24,25] Bisphosphonates work by several different mechanisms to reduce bone resorption and bone formation in cancers.[26-28] They are effective in cancer treatment by making the bone marrow a less favorable environment for cancer cell colonization by inhibiting the release of bone-derived growth factors and prostaglandins during bone resorption. They also interfere with the functions of bone marrow derived cells (mesenchymal cells, monocytes, macrophages, and progenitor cells)[29] that have an important role in priming distant tissues for tumor metastasis. They have also been shown to improve immune surveillance against neoplastic cells. Some authors suggested that BPs exhibit direct antitumor effects, especially when administered with cytotoxic agents.[8] Bisphosphonates reduce the breast cancer incidence in postmenopausal women by 30%.[30] *In vitro* work by Mundy et al[31] has shown that BPs may have a direct action on tumor cells by inducing apoptosis, inhibiting matrix metalloproteinase-1, and inhibiting adhesion of tumor cells within the bone.

Consensus guidelines indicate that all patients with multiple myeloma and radiologically confirmed bone metastases from breast cancer should receive BPs from the time of diagnosis and continued indefinitely.[32] The beneficial effect of BPs in patients with bone metastases secondary to other cancers including prostate cancer[33] and a broad range of other solid tumors including lung cancer[34] has also been demonstrated. Zoledronic acid, however, has proven effective across the range of solid tumors, whereas the efficacy of the other agents is restricted to breast cancer and myeloma.[35,36]

Hypercalcemia

Hypercalcemia is not a very common condition in orthopedic practice. It is usually seen in patients with metastatic bone disease, multiple myeloma, and primary hyperparathyroidism.[8] Mostly, it is due to calcium release from the bone by osteoclasts or metastatic tumor cells. Bisphosphonates are very effective in controlling osteoclast-mediated calcium release and hypercalcemia. A single infusion of zoledronic acid normalizes serum calcium level in 88% of cases in an average of 10 days.[37] The duration of the normocalcemic phase depends on the underlying disease, about 2 weeks in most cases. A second infusion may be required if serum calcium level rises again. For rapid normalization of hypercalcemia in life-threatening conditions, a combination of BPs with calcitonin is effective. It lowers the calcium level within hours by increasing renal calcium excretion.

Fibrous Dysplasia

Fibrous dysplasia is characterized by the production of fibrous tissue and woven bone that replaces the normal cortical bone. This abnormal bone leaves the skeleton weak and prone to fractures. In this disease, the fundamental defect is somatic mutation in the gene coding for the alpha subunit of Gs protein (the G protein that stimulates cAMP formation). This overproduction of cAMP in turn causes overexpression of c-fos, which plays an important role in regulating the interplay of osteoblastic and osteoclastic proliferation and differentiation, resulting in excessive osteoclastic activity. Bisphosphonates lead to thickening and progressive ossification radiologically and, improvement in pain and N-telopeptide levels. Most workers have used IV pamidronate,[38-44] with sporadic reports of use of combined pamidronate and oral alendronate[45] and only oral alendronate.[46]

Arthroplasty

Main objective of BPs in arthroplasty is to prevent aseptic loosening, periprosthetic osteoporosis, and fractures so as to reduce the frequency of further revision surgeries. Common reasons for revision are aseptic loosening, periprosthetic osteoporosis (stress shielding), wear debris-induced osteolysis, and periprosthetic fracture.[47]

Initially, it was thought that by inhibiting the bone remodeling, BPs will affect the bone in-growth in uncemented prosthesis and thus may affect implant-bone bonding. In clinical studies, however, many authors noted an improved periprosthetic bone density and reduced stress shielding after oral or local use of BPs. Many of them also found decreased rate of migration of the implants.[48-52] Bisphosphonates are also supposed to reduce osteoclastic activation and osteolysis induced by wear debris. Wang et al[52] reported that oral administration of alendronate for 6 months postoperatively significantly improved the bone mineral density in total knee arthroplasty (TKA) patients.

Heterotopic Calcification and Ossification

For the prophylaxis and treatment of heterotopic ossification, indomethacin is most commonly used and

found to be effective.[53] Other modality that has shown good result is radiotherapy, but it is not commonly used. Bisphosphonates experimentally inhibit the mineralization of soft tissues and heterotopic ossification,[54] but in clinical use, mixed results have been reported. Mavrogenis et al[55] found that BPs are prophylactically effective if started shortly after the trauma, but mineralization of the bone matrix resumes after drug discontinuation. Etidronate[56-59] is considered to be as effective as indomethacin but not cost-effective. Other BPs under trial are alendronate,[60,61] pamindronate,[62,63] and risendronate.[64]

Paget's Disease

In the present times, normalization of bone turnover is possible in almost all patients with the potent BPs available for clinical use. Modern BPs normalize the bone turnover and bone histology as well as lead to healing of lytic radiologic lesions.[65] Long-term follow-up data from the zoledronate demonstrate high response rates and very long durations of biochemical remission. Patient treated with this drug is unlikely to experience disease progression for greater than 6 years and therefore require less often follow-ups thus making therapy cost-effective and has beneficial effects on quality of life.

Complex Regional Pain Syndrome

The reflex sympathetic dystrophy (RSD) or complex regional pain syndrome-I (CRPS-I) is associated with increased bone resorption and patchy osteoporosis, which might benefit from treatment with BPs, powerful inhibitors of bone resorption. Due to still unknown etiology, multiple modalities have been used till date for treatment of RSD, including BPs. The role of BPs in treatment of RSD has been proven by clinical response with diminution in spontaneous pain, tenderness, swelling (circumference of the affected limb), and improvement in motion by reducing local acceleration of bone remodeling in many clinical studies.[66-71] Tran de et al[72] reviewed 41 randomized controlled trials and found that only BPs (oral alendronate and IV pamidronate) appear to offer clear benefits for patients with CRPS-I as compared with other treatments.

Avascular Necrosis of Femoral Head (AVNFH)

Use of BPs in AVNFH is still controversial. Bisphosphonates, especially alendronate, have been shown to decrease rate of progression of AVN lesions,[73-77] but the benefit is mostly in the pre-collapse stages. Hence, most authors recommend that therapy should be initiated in the early phases of AVN, as later stages appear to be less responsive to medication.[76,78]

BONE MARROW EDEMA SYNDROME

This is also known as idiopathic transient osteoporosis of the hip. It is most often seen in middle-aged men, but sometimes occurs in women (usually in late pregnancy) and is bilateral in one-third of the patients. It presents as increasing pain and limp with local muscle wasting. It is usually diagnosed by an abnormal bone scan and in later stage by radiologically visible osteoporosis in the region of femoral head and neck. Demineralization may not be apparent on plain radiographs for 6 weeks after onset of symptoms. Intravenous ibandronate combined with physical therapy and calcium, vitamin D supplementation have shown a significant improvement in hip score before and after treatment of these patients.[79,80]

Stress Fractures in Athletes

Stress fractures are a major problem for athletic and military populations. Reported incidences are 1.4% in collegiate athletes[81] and 8.4% among infantry units of the Finnish Army.[82]

Till date, there is still no conclusive evidence to prove any effect of BPs on stress fracture healing in humans.[83] Alendronate[84] and pamidronate[85] have shown some promise in initial studies, but larger studies need to be done to accept BPs as a treatment modality for stress fractures.

Perthe's Disease

Legg Calvé Perthes disease is a childhood form of osteonecrosis of the femoral head with a reported incidence of 8.5–21 per 100,000 children per year.[86] Little et al[87] showed that zoledronic acid improves femoral head sphericity in Perthe's disease in rats. McQuade et al[88] also found it useful in children with Perthe's disease. Recently, Fanord et al proved that BPs (alendronate) modified gold nanoparticles as a useful vehicle to study the treatment of osteonecrosis of the femoral head in *in vitro* models of Perthe's disease.[89]

ADVERSE EFFECTS

Gastrointestinal Side Effects

These side effects are predominantly seen with oral formulations (Table 2). Bisphosphonates affect all levels of the GI tract from the lower esophagus to the colon. Common side effects are mucositis, flatulence, and diarrhea. Less common side effects are erosion and ulceration in the esophagus, stomach, and duodenum.[90-92] These side effects may be avoided by adhering to dosing instructions.[93] Biswas et al in their observational study in 11,916 postmenopausal women found that the most common reasons for stopping alendronate therapy are

Table 2: Side effects of BPs

Side effects seen predominantly with oral formulations
1. Gastrointestinal toxicity
2. Esophageal erosions
3. Stomach upset
Side effects seen predominantly with parental formulations
1. Acute phase reaction
2. Renal toxicity
3. Osteonecrosis of jaw
4. Transient leukopenia
5. Bone pain
Side effects seen with both oral and parental formulations
1. Skin rash
2. Ocular complications
3. Hypocalcemia
4. Increased PTH levels
5. Atrial fibrillations
6. Altered taste
7. Precipitation of asthma

dyspepsia, esophagitis, esophageal reflux, duodenitis, gastritis, heart burn, or nausea.[94] Diarrhea is more common with the use of older non-nitrogen containing BPs.[95] Reszka et al[96] proposed that the basic reason for these GI side effects is inhibition of the mevalonate pathway by nitrogen-containing BPs that in turn compromise mucosal healing through effects on the keratinocytes in a dose-dependent manner. Lichtenberger et al[97] proposed that these effects are because of weakening the mucosal hydrophobic barrier that may trigger the development of mucosal injury and possible ulceration. They also demonstrated that the variable toxicity of BPs to the antral mucosa appears to be associated with their ability to compromise the surface hydrophobic phospholipid barrier of the tissue, with pamidronate>>>alendronate>risedronate.

The best way to minimize these side effects is to properly explain to the patient that these medications should be taken empty stomach with a glass full of water (130–240 ml) and that they should remain upright for at least 30–60 minutes and then only take their breakfast.[93]

Acute Phase Reaction and Musculoskeletal Pain

This side effect is basically a spectrum of various flu-like signs and symptoms, particularly mild fever (up to 38°C), weakness and exhaustion, leukocytosis, myalgia, and bone pain. These symptoms are reported commonly with use of IV formulations of amino-BPs[98,99] and after the first infusion. They generally resolve within 48 hours and respond well to nonsteroidal anti-inflammatory drugs (NSAIDs) and antipyretic measures. Most authors relate this with transient release of pyrogenic cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α).[93] The frequency and severity of acute-phase reactions to different BPs reported in clinical trials appear to vary markedly. Acute-phase reactions occur only with IV amino-BPs and may be more common with zoledronic acid.[93] These are thought to occur because of their potential to activate human T cells.[100] Notably, these symptoms do not recur with subsequent infusions.

Bisphosphonates-related Osteonecrosis of the Jaw (BRONJ)

This condition was reported first by Marx (2003)[101] in 36 patients, soon after the introduction of zoledronic acid. All patients had received high doses of IV BPs for skeletal complications of malignancy. Subsequently, this condition was also reported with use of lower doses of BPs as in osteoporosis,[102,103] but even in these series, 90% of cases were cancer patients. As per the working definition of BRONJ, following criteria should be fulfilled: Current or previous exposure to BPs; exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and no history of radiotherapy to the jaws.[104]

The exact incidence of BRONJ is still unknown. The estimated incidence of BRONJ is from 0.8 to 12% with IV BPs.[104] Other studies also indicate that nearly 95% of patients diagnosed with BRONJ are cancer patients who received more potent nitrogen-substituted IV BPs.[105] Ruggiero et al[102] in their retrospective analysis of patients with BRONJ found that only 11% of all patients were treated with chronic oral BPs and the rest received IV BPs. Dental interventions, such as tooth extractions, dental implants, or trauma from dentures along with poor periodontal status increase the risk of developing BRONJ.[101,106,107]

Most of the reports of BRONJ are associated with malignancies, such as multiple myeloma or breast cancer.[106,108,109] Durie et al[110] reported the incidence of jaw osteonecrosis in myeloma patient as 3% with pamidronate and 10% with zolindronic acid at 36 months of therapy.

This is very surprising that BRONJ was identified mostly in individual case reports and case series and also in retrospective studies but not identified in any prospective clinical trials. In prospective clinical trials for osteoporosis or Paget's disease with more than 60,000 patient-years, Bilezikian et al were unable to find BRONJ. HORIZON trial by Black et al[19] with IV zoledronic acid for osteoporosis found only two patients of osteonecrosis on retrospective review, one in the treatment group, and another in the placebo group. Recently, Borromeo et al[111] in their case–control study found significant association of osteonecrosis of jaw with BPs treatment.

Atrial Fibrillation (AF)

The first report of increased chances of AF came from fracture intervention trial (FIT) by Merck et al in 1997. They found 47 (1.5%) serious AF adverse events among

patients receiving alendronate *vs* 31 (1.0%) among those receiving placebo during an average of 4 years. This was not statistically significant and alendronate was considered to be safe from this point of view. In year 2007, a randomized controlled trial by Black et al[19] demonstrated a significant risk of serious AF with IV zolindronic acid. Other studies either showed a nonsignificant trend[112] or even contradictory results.[20] Recently, a meta-analysis of RCTs by Mak et al[113] revealed only a trend of higher AF risk in BP users than in patients on placebo. They concluded that there is no evidence of a higher risk of AF associated with BP use, but there is a probability of development of AF (this is 0.484 if the risk of AF was estimated to be more than 20%). Lewiecki et al[114] in their pooled analysis of four ibandronate pivotal trials found that ibandronate is not associated with an increased incidence of AF. Similarly, many other authors were also unable to find any a significant correlation between BPs and AF.[115-122]

Esophageal Cancer

There is lot of confusion in literature regarding this side effect. Green et al[123] found an increased risk (almost double) of esophageal cancers with BPs use for more than 3 years (in most cases 5 years). They found that the risk increased to 2/1000 from 1/1000 in a control population of age 60 to 79 years. In another study from the same population, Cardwell et al[124] were unable to find this increased risk. They reported a combined incidence of 0.7 per 1000 person-years of risk for esophageal and gastric cancer in both the BP and control cohorts; the incidence of esophageal cancer alone in the BP and control cohorts was 0.48 and 0.44 per 1000 person-years of risk, respectively. There was no difference in the risk of esophageal and gastric cancer combined between the cohorts for any BP use or risk of esophageal cancer only. Recently, Wysowski[125] addressed this issue and opined that the major difference in the two studies was the length of follow-up, with the negative study having 4.5 years and the positive one 7.7 years. The positive study also had an adequate sample size, control group, and adjustment for covariates (age; sex; smoking status; alcohol drinking; body mass index; diagnosis of osteoporosis; previous fracture; upper GI disease; and prescription of NSAIDs, corticosteroids, or acid suppressants). However, neither study validated diagnoses by medical records nor provided information on whether drugs were taken according to directions. It is now general consensus that further studies are needed on this area to confirm any of the results.[126-128]

Renal Safety

Renal side effects of BPs are mostly dose dependent. When BPs are given to patients either orally or parenterally, part of the drug is taken up by the tissues and the rest is excreted unchanged via the kidneys. Increasing the BP dose leads to an increase in the amount of drug measured in the urine. This linear relation is maintained only up to a certain point, after which further dose escalation leads to a relative decrease in the renal excretion.[93] Most of the reports of this side effect come from more frequent IV doses of BPs as used in cancer treatment (zoledronic acid >> pamidronate), not seen with standard oral doses used in prevention of osteoporosis.[129-138] The renal safety profile of IV ibandronate and all oral BPs is similar to that of placebo.[93,139,140]

Atypical Fractures

On literature review, we found numerous case reports describing unusual low-energy subtrochanteric femoral fractures and pelvic insufficiency fractures in patients with long-term BP treatment. These reports are presumed to be because of the prolonged suppression of bone metabolism and problems with bone healing.[141-152] These fractures are typically associated with prodromal pain in the region of the fracture and have characteristic radiographic findings, including cortical hypertrophy, a transverse and low oblique fracture pattern with medial cortical spiking. Sometimes, these fractures are bilateral.[151-155] These patients usually show severe suppression of bone turnover on bone biopsy,[154-161] though normal biopsy has also been reported.[11] Similar conclusions have also been drawn by Tucci et al,[162], Schilcher et al,[163] Gunawardena et al,[164] and Giusti et al. [165] Czerwinskihas estimated these fractures to be very rare (2.3 per 10,000 patient-years). Other authors also suggest that the number of fractures prevented by BP therapy far exceeds the number of atypical femoral fractures potentially related to BPs; so, there is no rationale in stopping the therapy.[22,166,167]

SUMMARY AND CONCLUSION

Newer BPs available for clinical use are very potent in their action and have fewer side effects. These can be given orally on daily, weekly, and monthly basis or intravenously on quarterly and yearly basis. These agents have been proven safe and effective for the prevention and treatment of osteoporosis with broad spectrum of action in fracture-risk reduction (i.e., spine, hip, and nonvertebral fractures). They are also very effective in Paget's disease and fibrous dysplasia. Now increasing evidences are available for their use in CRPS I, AVNFH, stress fractures, and many other conditions. These agents have a special place in the treatment of solid cancers, metastatic bone diseases, and hypercalcemia of malignancy. There are ongoing studies to prove their effectiveness in childhood diseases such as Perthe's

disease and in heterotropic calcification. There is some evidence for their effectiveness in prevention of bone collapse following AVNFH and in enhancing implant fixation with a decreased rate of osteolysis following arthroplasty.

REFERENCES

1. Ghinoi V, Brandi ML. Clodronate: mechanisms of action on bone remodelling and clinical use in osteometabolic disorders. Expert Opin Pharmacother 2002 Nov;3(11): 1643-1656.
2. Cremers S, Papapoulos S. Pharmacology of bisphosphonates. Bone 2011 Jul;49(1):42-49.
3. Papapoulos SE. Bisphosphonates: how do they work? Best Pract Res Clin Endocrinol Metab 2008 Oct;22(5):831-847.
4. Papapoulos S, Makras P. Selection of antiresorptive or anabolic treatments for postmenopausal osteoporosis. Nat Clin Pract Endocrinol Metab 2008 Sep;4(9):514-523.
5. Borah B, Dufresne TE, Chmielewski PA, Gross GJ, Prenger MC, Phipps RJ. Risedronate preserves trabecular architecture and increases bone strength in vertebra of ovariectomized minipigs as measured by three-dimensional microcomputed tomography. J Bone Miner Res 2002 Jul;17(7):1139-1147.
6. McClung MR. Bisphosphonates in osteoporosis: recent clinical experience. Expert Opin Pharmacother 2000 Jan;1(2): 225-238.
7. Morris CD, Einhorn TA. Bisphosphonates in orthopaedic surgery. J Bone Joint Surg Am 2005 Jul;87(7):1609-1618.
8. Bartl R, Bartl C, Gradinger R. Use of bisphosphonates in orthopedic surgery. Orthopade 2008 Jun;37(6):595-613.
9. Luckman SP, Hughes DE, Coxon FP, Graham R, Russell G, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. J Bone Miner Res 1998 Apr;13(4):581-589.
10. Russell R, Watts N, Ebetino F, Rogers M. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporosis Int 2008;19(6):733-759.
11. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010 Apr;95(4): 1555-1565.
12. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004 Mar 18;350(12):1189-1199.
13. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006 Dec 27;296(24):2927-2938.
14. Lozano-Calderon SA, Colman MW, Raskin KA, Hornicek FJ, Gebhardt M. Use of bisphosphonates in orthopedic surgery: pearls and pitfalls. Orthop Clin North Am 2014 Jul;45(3): 403-416.
15. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008 Apr;19(4):399-428.
16. Canalis E, Mazziotti G, Giustina A, Bilezikian J. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 2007;18(10):1319-1328.
17. Olszynski W, Davison K. Alendronate for the treatment of osteoporosis in men. Expert Opin Pharmacother 2008;9: 491-498.
18. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000 Aug 31;343(9):604-610.
19. Black D, Delmas P, Eastell R, Reid I, Boonen S, Cauley J, Cosman F, Lakatos P, Leung PC, Man Z, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med2007 May 3;356(18):1809-1822.
20. Lyles K, Colon-Emeric C, Magaziner J, Adachi J, Pieper C, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007 Nov 1;357(18):1799-1809.
21. Balink H. Shin splints: an unexpected effect of bisphosphonates in osteogenesis imperfecta. Clin Nucl Med 2009 Feb;34(2): 87-88.
22. Black DM, Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, Cauley J, Leung PC, Boonen S, Santora A, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med 2010 May 13;362(19):1761-1771.
23. Green JR. Antitumor effects of bisphosphonates. Cancer 2003 Feb 1;97(3 Suppl):840-847.
24. Clezardin P. The antitumor potential of bisphosphonates. Semin Oncol 2002 Dec;29(6 Suppl 21):33-42.
25. Lee MV, Fong EM, Singer FR, Guenette RS. Bisphosphonate treatment inhibits the growth of prostate cancer cells. Cancer Res 2001 Mar 15;61(6):2602-2608.
26. Body JJ, Bartl R, Burckhardt P, Delmas PD, Diel IJ, Fleisch H, Kanis JA, Kyle RA, Mundy GR, Paterson AH, et al. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. J Clin Oncol 1998 Dec;16(12): 3890-3899.
27. Fleisch H. Bisphosphonates: mechanisms of action. Endocr Rev 1998 Feb;19(1):80-100.
28. Francis MD, Russell RG, Fleisch H. Diphosphonates inhibit formation of calcium phosphate crystals in vitro and pathological calcification in vivo. Science 1969 Sep 19;165(899): 1264-1266.
29. Kaplan RN, Psaila B, Lyden D. Bone marrow cells in the 'pre-metastatic niche': within bone and beyond. Cancer Metastasis Rev 2006 Dec;25(4):521-529.
30. Chlebowski RT, Chen Z, Cauley JA, Anderson G, Rodabough RJ, McTiernan A, Lane DS, Manson JE, Snetselaar L, Yasmeen S, et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 2010 Aug 1;28(22): 3582-3590.
31. Mundy GR, Yoneda T, Hiraga T. Preclinical studies with zoledronic acid and other bisphosphonates: impact on the bone microenvironment. Semin Oncol 2001 Apr;28(2 Suppl 6):35-44.
32. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, Crino L, Dirix L, Gnant M, Gralow J, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol. 2008 Mar;19(3):420-432.
33. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Zheng M. Long-term efficacy of zoledronic acid for the prevention of skeletal

complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004 Jun 2;96(11):879-882.
34. Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M, Pawlicki M, De Souza P, Zheng M, Urbanowitz G, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004 Jun 15;100(12):2613-2621.
35. Coleman RE. Adjuvant bisphosphonates in breast cancer: are we witnessing the emergence of a new therapeutic strategy? Eur J Cancer 2009 Jul;45(11):1909-1915.
36. Coleman RE, McCloskey EV. Bisphosphonates in oncology. Bone 2011 Jul;49(1):71-76.
37. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001 Jan 15;19(2):558-567.
38. DiMeglio LA. Bisphosphonate therapy for fibrous dysplasia. Pediatr Endocrinol Rev 2007 Aug;4 (Suppl 4):440-445.
39. Kochar IP, Kulkarni KP. Pamidronate for fibrous dysplasia due to McCune Albright Syndrome. Indian Pediatr 2010 Jul 7;47(7):633-635.
40. Lala R, Matarazzo P, Andreo M, Marzari D, Bellone J, Corrias A, de Santis C. Bisphosphonate treatment of bone fibrous dysplasia in McCune-Albright syndrome. J Pediatr Endocrinol Metab 2006 May;19 (Suppl 2):583-593.
41. Matarazzo P, Lala R, Masi G, Andreo M, Altare F, de Sanctis C. Pamidronate treatment in bone fibrous dysplasia in children and adolescents with McCune-Albright syndrome. J Pediatr Endocrinol Metab 2002;15 (Suppl 3):929-937.
42. Parisi MS, Oliveri MB, Mautalen CA. Bone mineral density response to long-term bisphosphonate therapy in fibrous dysplasia. J Clin Densitom 2001 Summer;4(2):167-172.
43. Plotkin H, Rauch F, Zeitlin L, Munns C, Travers R, Glorieux FH. Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. J Clin Endocrinol Metab 2003 Oct;88(10):4569-4575.
44. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. J Pediatr 2000 Sep;137(3): 403-409.
45. Lane JM, Khan SN, O'Connor WJ, Nydick M, Hommen JP, Schneider R, Tomin E, Brand J, Curtin J. Bisphosphonate therapy in fibrous dysplasia. Clin Orthop Relat Res 2001 Jan;382:6-12.
46. Khadilkar VV, Khadilkar AV, Maskati GB. Oral bisphosphonates in polyostotic fibrous dysplasia. Indian Pediatr 2003 Sep;40(9):894-846.
47. Sundfeldt M, Carlsson LV, Johansson CB, Thomsen P, Gretzer C. Aseptic loosening, not only a question of wear: a review of different theories. Acta Orthop 2006 Apr;77(2):177-197.
48. Bhandari M, Bajammal S, Guyatt GH, Griffith L, Busse JW, Schunemann H, Einhorn TA. Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty. A meta-analysis. J Bone Joint Surg Am 2005 Feb;87(2):293-301.
49. Hilding M, Aspenberg P. Local peroperative treatment with a bisphosphonate improves the fixation of total knee prostheses: a randomized, double-blind radiostereometric study of 50 patients. Acta Orthop 2007 Dec;78(6):795-799.
50. Bobyn JD, Hacking SA, Krygier JJ, Harvey EJ, Little DG, Tanzer M. Zoledronic acid causes enhancement of bone growth into porous implants. J Bone Joint Surg Br 2005 Mar;87(3):416-420.
51. Tanzer M, Karabasz D, Krygier JJ, Cohen R, Bobyn JD. The Otto Aufranc Award: bone augmentation around and within porous implants by local bisphosphonate elution. Clin Orthop Relat Res 2005 Dec;441:30-39.
52. Wang CJ, Wang JW, Weng LH, Hsu CC, Huang CC, Chen HS. The effect of alendronate on bone mineral density in the distal part of the femur and proximal part of the tibia after total knee arthroplasty. J Bone Joint Surg Am 2003 Nov;85(11): 2121-2126.
53. Haran MJ, Bhuta T, Lee BS. WITHDRAWN: Pharmacological interventions for treating acute heterotopic ossification. Cochrane Database Syst Rev 2010(5):CD003321.
54. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. Ann Pharmacother 2005 Apr;39(4):668-677.
55. Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification revisited. Orthopedics 2011 Mar;34(3):177.
56. Vasileiadis GI, Sakellariou VI, Kelekis A, Galanos A, Soucacos PN, Papagelopoulos PJ, Babis GC. Prevention of heterotopic ossification in cases of hypertrophic osteoarthritis submitted to total hip arthroplasty. Etidronate or Indomethacin? J Musculoskelet Neuronal Interact 2010 Jun;10(2):159-165.
57. Shafer DM, Bay C, Caruso DM, Foster KN. The use of eidronate disodium in the prevention of heterotopic ossification in burn patients. Burns 2008 May;34(3):355-360.
58. Haran M, Bhuta T, Lee B. Pharmacological interventions for treating acute heterotopic ossification. Cochrane Database Syst Rev 2004 (4):CD003321.
59. Yutani Y, Ohashi H, Nishimura N, Yamano Y. Clinical effect of etidronate disodium (EHDP) on heterotopic ossification following total hip arthroplasty. Osaka City Med J 1995 Dec;41(2):63-73.
60. Ben Hamida KS, Hajri R, Kedadi H, Bouhaouala H, Salah MH, Mestiri A, Zakraoui L, Doughi MH. Myositis ossificans circumscripta of the knee improved by alendronate. Joint Bone Spine 2004 Mar;71(2):144-146.
61. Yaffe A, Kollerman R, Bahar H, Binderman I. The influence of alendronate on bone formation and resorption in a rat ectopic bone development model. J Periodontol 2003 Jan;74(1):44-50.
62. Hou JW. Progressive osseous heteroplasia controlled by intravenous administration of pamidronate. Am J Med Genet A 2006 Apr15;140(8):910-913.
63. Schuetz P, Mueller B, Christ-Crain M, Dick W, Haas H. Amino-bisphosphonates in heterotopic ossification: first experience in five consecutive cases. Spinal Cord 2005 Oct;43(10):604-610.
64. Fujii N, Hamano T, Isaka Y, Ito T, Imai E. Risedronate: a possible treatment for extraosseous calcification. Clin Calcium 2005 Sep;15 (Suppl 1):75-78.
65. Reid IR, Nicholson GC, Weinstein RS, Hosking DJ, Cundy T, Kotowicz MA, Murphy WA Jr, Yeap S, Dufresne S, Lombardi A, et al. Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. Am J Med 1996 Oct;101(4):341-348.
66. Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex regional pain syndrome: a review. Ann Vasc Surg 2008 Mar;22(2):297-306.
67. Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997 Mar;56(3):201-204.

68. Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. Arthritis Rheum 2004 Nov;50(11):3690-3697.
69. Chauvineau V, Codine P, Herisson C, Pellas F, Pelissier J. What is the place of diphosphonates in the treatment of complex regional pain syndrome I? Ann Readapt Med Phys 2005 Apr;48(3):150-157.
70. Schott GD. Bisphosphonates for pain relief in reflex sympathetic dystrophy? Lancet 1997 Oct 18;350(9085):1117.
71. Simm PJ, Briody J, McQuade M, Munns CF. The successful use of pamidronate in an 11-year-old girl with complex regional pain syndrome: response to treatment demonstrated by serial peripheral quantitative computerised tomographic scans. Bone 2010 Apr;46(4):885-888.
72. Tran de QH, Duong S, Bertini P, Finlayson RJ. Treatment of complex regional pain syndrome: a review of the evidence. Can J Anaesth. 2010 Feb;57(2):149-166.
73. Wilkinson JM, Little DG. Bisphosphonates in orthopedic applications. Bone 2011 Jul;49(1):95-102.
74. Cardozo JB, Andrade DM, Santiago MB. The use of bisphosphonate in the treatment of avascular necrosis: a systematic review. Clin Rheumatol 2008 Jun;27(6):685-688.
75. Glimcher MJ, Kenzora JE. Nicolas Andry award. The biology of osteonecrosis of the human femoral head and its clinical implications: 1. Tissue biology. Clin Orthop Relat Res 1979 Jan-Feb(138):284-309.
76. Tarner IH, Dinser R, Muller-Ladner U. Pharmacotherapeutic aspects of femoral head necrosis. Orthopade 2007 May;36(5): 446-450.
77. Tagil M, Astrand J, Westman L, Aspenberg P. Alendronate prevents collapse in mechanically loaded osteochondral grafts: a bone chamber study in rats. Acta Orthop Scand 2004 Dec;75(6):756-761.
78. Lai KA, Shen WJ, Yang CY, Shao CJ, Hsu JT, Lin RM. The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis. A randomized clinical study. J Bone Joint Surg Am 2005 Oct;87(10): 2155-2159.
79. Li JF, Yan JY. Diagnosis and treatment of bone marrow edema syndrome of the hip and differential diagnosis from avascular necrosis of femoral head. Zhongguo Gu Shang 2009 Sep;22(9):697-699.
80. Ringe JD, Dorst A, Faber H. Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate. Osteoporos Int 2005 Dec;16(12):2063-2068.
81. Hame SL, LaFemina JM, McAllister DR, Schaadt GW, Dorey FJ. Fractures in the collegiate athlete. Am J Sports Med 2004 Mar;32(2):446-451.
82. Ward K, Cowell CT, Little DG. Quantification of metaphyseal modeling in children treated with bisphosphonates. Bone 2005 Jun;36(6):999-1002.
83. Milgrom C, Finestone A, Novack V, Pereg D, Goldich Y, Kreiss Y, Zimlichman E, Kaufman S, Liebergall M, Burr D. The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone 2004 Aug;35(2): 418-424.
84. Barrett JG, Sample SJ, McCarthy J, Kalscheur VL, Muir P, Prokuski L. Effect of short-term treatment with alendronate on ulnar bone adaptation to cyclic fatigue loading in rats. J Orthop Res 2007 Aug;25(8):1070-1077.
85. Stewart GW, Brunet ME, Manning MR, Davis FA. Treatment of stress fractures in athletes with intravenous pamidronate. Clin J Sport Med 2005 Mar;15(2):92-94.
86. Kim HK, Randall TS, Bian H, Jenkins J, Garces A, Bauss F. Ibandronate for prevention of femoral head deformity after ischemic necrosis of the capital femoral epiphysis in immature pigs. J Bone Joint Surg Am 2005 Mar;87(3):550-557.
87. Little DG, McDonald M, Sharpe IT, Peat R, Williams P, McEvoy T. Zoledronic acid improves femoral head sphericity in a rat model of perthes disease. J Orthop Res 2005 Jul;23(4):862-868.
88. McQuade M, Houghton K. Use of bisphosphonates in a case of Perthes disease. Orthop Nurs 2005 Nov-Dec;24(6):393-398.
89. Fanord F, Fairbairn K, Kim H, Garces A, Bhethanabotla V, Gupta VK. Bisphosphonate-modified gold nanoparticles: a useful vehicle to study the treatment of osteonecrosis of the femoral head. Nanotechnology 2011 Jan 21;22(3):035102.
90. de Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D, Pryor-Tilloston S, Seleznick MJ, Pinkas H, Wang KK. Esophagitis associated with the use of alendronate. N Engl J Med 1996 Oct 3;335(14):1016-1021.
91. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. Int J Clin Pract (Suppl) 1999 Apr;101: 51-61.
92. Marshall JK. The gastrointestinal tolerability and safety of oral bisphosphonates. Expert Opin Drug Saf 2002 May;1(1):71-78.
93. Diel IJ, Bergner R, Grotz KA. Adverse effects of bisphosphonates: current issues. J Support Oncol 2007 Nov-Dec;5(10): 475-482.
94. Biswas PN, Wilton LV, Shakir SA. Pharmacovigilance study of alendronate in England. Osteoporos Int 2003 Jul;14(6):507-514.
95. Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. Dig Dis Sci 2002 Aug;47(8):1665-1678.
96. Reszka AA, Halasy-Nagy J, Rodan GA. Nitrogen-bisphosphonates block retinoblastoma phosphorylation and cell growth by inhibiting the cholesterol biosynthetic pathway in a keratinocyte model for esophageal irritation. Mol Pharmacol 2001 Feb;59(2):193-202.
97. Lichtenberger LM, Romero JJ, Gibson GW, Blank MA. Effect of bisphosphonates on surface hydrophobicity and phosphatidylcholine concentration of rodent gastric mucosa. Dig Dis Sci 2000 Sep;45(9):1792-1801.
98. Hortobagyi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoff C, Wheeler H, Simeone JF, Seaman JJ, Knight RD, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998 Jun;16(6):2038-2044.
99. Pecherstorfer M, Jilch R, Sauty A, Horn E, Keck AV, Zimmer-Roth I, Thiebaud D. Effect of first treatment with aminobisphosphonates pamidronate and ibandronate on circulating lymphocyte subpopulations. J Bone Miner Res 2000 Jan;15(1):147-154.
100. Thompson K, Rogers MJ. Statins prevent bisphosphonate-induced gamma,delta-T-cell proliferation and activation *in vitro*. J Bone Miner Res 2004 Feb;19(2):278-288.
101. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003 Sep;61(9):1115-1117.
102. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004 May;62(5):527-534.

103. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006 May 16;144(10):753-761.
104. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007 Mar;65(3):369-376.
105. Goytia RN, Salama A, Khanuja HS. Bisphosphonates and osteonecrosis: potential treatment or serious complication? Orthop Clin North Am 2009 Apr;40(2):223-234.
106. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008 Jun;23(6):826-836.
107. Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst 2007 Jul 4;99(13):1016-1024.
108. Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. Med J Aust 2005 Apr 18;182(8):417-418.
109. Bagan JV, Murillo J, Jimenez Y, Poveda R, Milian MA, Sanchis JM, Silvestre FJ, Scully C. Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. J Oral Pathol Med 2005 Feb;34(2):120-123.
110. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005 Jul 7;353(1):99-102.
111. Borromeo GL, Brand C, Clement JG, McCullough M, Thomson W, Flitzanis E, Wark JD. Is bisphosphonate therapy for benign bone disease associated with impaired dental healing? A case-controlled study. BMC Musculoskelet Disord 2011;12:71.
112. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. N Engl J Med 2007 May 3;356(18): 1895-1896.
113. Mak A, Cheung M, Ho R, Cheak A, Lau C. Bisphosphonates and atrial fibrillation: Bayesian meta-analyses of randomized controlled trials and observational studies. BMC Musculoskelet Disord 2009;10(1):113.
114. Lewiecki EM, Cooper C, Thompson E, Hartl F, Mehta D, Papapoulos SE. Ibandronate does not increase risk of atrial fibrillation in analysis of pivotal clinical trials. Int J Clin Pract 2010 May;64(6):821-826.
115. Sewerynek E, Stuss M. Bisphosphonates and the risk of atrial fibrillation. Endokrynol Pol 2011 Jan-Feb;62(1):93-96.
116. Rhee CW, Lee J, Oh S, Choi NK, Park BJ. Use of bisphosphonate and risk of atrial fibrillation in older women with osteoporosis. Osteoporos Int 2012 Jan;23(1):247-254.
117. Pazianas M, Cooper C, Wang Y, Lange JL, Russell RG. Atrial fibrillation and the use of oral bisphosphonates. Ther Clin Risk Manag 2011;7:131-144.
118. Barrett-Connor E, Swern AS, Hustad CM, Bone HG, Liberman UA, Papapoulos S, Wang H, de Papp A, Santora AC. Alendronate and atrial fibrillation: a meta-analysis of randomized placebo-controlled clinical trials. Osteoporos Int 2012 Jan;23(1):233-245.
119. Arslan C, Aksoy S, Dizdar O, Dede DS, Harputluoglu H, Altundag K. Zoledronic acid and atrial fibrillation in cancer patients. Support Care Cancer 2011 Mar;19(3):425-430.
120. Wilkinson GS, Baillargeon J, Kuo YF, Freeman JL, Goodwin JS. Atrial fibrillation and stroke associated with intravenous bisphosphonate therapy in older patients with cancer. J Clin Oncol 2010 Nov 20;28(33):4898-4905.
121. Vestergaard P, Schwartz K, Pinholt EM, Rejnmark L, Mosekilde L. Risk of atrial fibrillation associated with use of bisphosphonates and other drugs against osteoporosis: a cohort study. Calcif Tissue Int 2010 May;86(5):335-342.
122. Pazianas M, Compston J, Huang CL. Atrial fibrillation and bisphosphonate therapy. J Bone Miner Res 2010 Jan;25(1):2-10.
123. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010;341:c4444.
124. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA 2010 Aug 11;304(6):657-663.
125. Wysowski DK. Oral bisphosphonates and oesophageal cancer. BMJ 2010;341:c4506.
126. Rozenberg S, Dutton S. Bisphosphonates and oesophageal cancer risk: where are we now? Maturitas 2011 Feb;68(2): 106-108.
127. Dixon WG, Solomon DH. Bisphosphonates and esophageal cancer--a pathway through the confusion. Nat Rev Rheumatol 2011 Jun;7(6):369-372.
128. Kuehn BM. Prolonged bisphosphonate use linked to rare fractures, esophageal cancer. JAMA 2010 Nov 17;304(19): 2114-2115.
129. Body JJ. Bisphosphonates in metastatic bone disease: renal safety matters. Oncologist 2005;10(Suppl 1):1-2.
130. Lewiecki EM. Safety of long-term bisphosphonate therapy for the management of osteoporosis. Drugs 2011 Apr 16;71(6): 791-814.
131. Bonomi M, Nortilli R, Molino A, Sava T, Santo A, Caldara A, Cetto GL. Renal toxicity and osteonecrosis of the jaw in cancer patients treated with bisphosphonates: a long-term retrospective analysis. Med Oncol 2010 Jun;27(2):224-229.
132. Recker RR, Lewiecki EM, Miller PD, Reiffel J. Safety of bisphosphonates in the treatment of osteoporosis. Am J Med 2009 Feb;122(2 Suppl):S22-S32.
133. Ott SM, Drueke T, Elder G, Fukagawa M, Jorgetti V, Langman CB, Moe S, McCann L, Wang AY, Weisinger J, et al. Renal function and bisphosphonate safety. J Bone Miner Res 2008 Mar;23(3):453-454.
134. Lafage-Proust MH. Once-yearly intravenous zoledronate does not impair renal function in postmenopausal women. Kidney Int 2008 Sep;74(5):557-559.
135. Dincer M, Altundag K, Harputluoglu H, Aksoy S, Cengiz M, Gullu I. Renal safety of zoledronic acid administration beyond 24 months in breast cancer patients with bone metastases. Med Oncol 2008;25(3):356-359.
136. Boonen S, Sellmeyer DE, Lippuner K, Orlov-Morozov A, Abrams K, Mesenbrink P, Eriksen EF, Miller PD. Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women. Kidney Int 2008 Sep;74(5):641-648.
137. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007 May 3;356(18):1809-822.
138. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res 2005 Dec;20(12):2105-2115.
139. Lyubimova NV, Kushlinsky NE, Lichinitser MR, Schlosser K. Renal safety of intravenous ibandronic Acid in breast cancer patients with metastatic bone disease. Clin Drug Investig 2003;23(11):707-716.

140. Jackson GH. Renal safety of ibandronate. Oncologist 2005;10 (Suppl 1):14-18.
141. Odvina CV, Levy S, Rao S, Zerwekh JE, Rao DS. Unusual mid-shaft fractures during long-term bisphosphonate therapy. Clin Endocrinol (Oxf) 2010 Feb;72(2):161-168.
142. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics 2006 Jan;61(1):31-33.
143. Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest 2007 Jul-Aug;30(7):590-597.
144. Imai K, Yamamoto S, Anamizu Y, Horiuchi T. Pelvic insufficiency fracture associated with severe suppression of bone turnover by alendronate therapy. J Bone Miner Metab 2007;25(5):333-336.
145. Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Lorich DG, Lane JM. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int 2009 Aug;20(8):1353-1362.
146. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma 2008 May-Jun;22(5):346-350.
147. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med 2008 Mar 20;358(12):1304-1306.
148. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury 2008 Feb;39(2):224-231.
149. Lee P, Seibel MJ. More on atypical fractures of the femoral diaphysis. N Engl J Med 2008 Jul 17;359(3):317.
150. Armamento-Villareal R, Napoli N, Panwar V, Novack D. Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. N Engl J Med 2006 Nov 9;355(19): 2048-2050.
151. Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. J Bone Miner Res 2009 Oct;24(10): 1736-1740.
152. Puhaindran ME, Farooki A, Steensma MR, Hameed M, Healey JH, Boland PJ. Atypical subtrochanteric femoral fractures in patients with skeletal malignant involvement treated with intravenous bisphosphonates. J Bone Joint Surg Am 2011 Jul 6;93(13):1235-1242.
153. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. J Bone Joint Surg Am 2009 Nov;91(11): 2556-2561.
154. Lee JK. Bilateral atypical femoral diaphyseal fractures in a patient treated with alendronate sodium. Int J Rheum Dis 2009 Jul;12(2):149-154.
155. Puah KL, Tan MH. Bisphosphonate-associated atypical fracture of the femur: Spontaneous healing with drug holiday and re-appearance after resumed drug therapy with bilateral simultaneous displaced fractures–a case report. Acta Orthop 2011 Jun;82(3):380-382.
156. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab 2008 Aug;93(8):2948-2952.
157. Miller PD. Is there a role for bisphosphonates in chronic kidney disease? Semin Dial 2007 May-Jun;20(3):186-190.
158. Miller PD. Diagnosis and treatment of osteoporosis in chronic renal disease. Semin Nephrol 2009 Mar;29(2):144-155.
159. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res. 2000 Apr;15(4):613-620.
160. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 2009 Jun;24(6):1095-1102.
161. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005 Mar;90(3):1294-1301.
162. Tucci JR. Effect of inappropriate and continuous therapy with alendronate for ten years on skeletal integrity–observations in two elderly patients. J Endocrinol Invest 2008 Mar;31(3):251-254.
163. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 2011 May 5;364(18):1728-1737.
164. Gunawardena I, Baxter M, Rasekh Y. Bisphosphonate-related subtrochanteric femoral fractures. Am J Geriatr Pharmacother 2011 Jun;9(3):194-198.
165. Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. Bone 2011 May 1;48(5):966-971.
166. Audran M, Cortet B, Thomas T. What do we know about atypical femoral fractures? Insights and enigmas. Joint Bone Spine 2011 Dec;78(6):568-571.
167. Nieves JW, Cosman F. Atypical subtrochanteric and femoral shaft fractures and possible association with bisphosphonates. Curr Osteoporos Rep 2010 Mar;8(1):34-39.