Knee Surg Sports Traumatol Arthrosc
DOI 10.1007/s00167-008-0673-0

SPORTS MEDICINE

Use of bisphosphonates for the treatment of stress fractures in athletes

Yosuke Shima · Lars Engebretsen · Junji Iwasa · Katsuhiko Kitaoka · Katsuro Tomita

Received: 11 March 2008 / Accepted: 5 November 2008

Abstract A literature review was performed to investigate the potential role of bisphosphonates for the treatment of stress fractures in athletes. Given the inhibitory action on osteoclast-mediated bone resorption, short-term suppression of bone remodeling using bisphosphonates could potentially treat stress fractures and prevent stress fractures from becoming regular fractures. To date, while there are some animal studies showing the scientific basis of bisphosphonates on stress fractures, there is still no conclusive evidence to prove any effect of bisphosphonates on stress fracture healing in humans. Further well-designed clinical trials should be carried out to establish their usefulness and safety. Until the results are available, it is prudent to limit the use of bisphosphonates for the treatment of stress fractures.

Keywords Bisphosphonates · Treatment · Stress fracture · Microdamage · Bone remodeling

Y. Shima · J. Iwasa
Oslo Sports Trauma Research Center,
Norwegian School of Sport Sciences,
P.O. Box 4014, Ullevaal Stadion 0806 Oslo, Norway
e-mail: s-yokke@hotmail.co.jp

L. Engebretsen (✉)
Orthopedic Center, Ullevaal University Hospital,
0407 Oslo, Norway
e-mail: lars.engebretsen@medisin.uio.no

L. Engebretsen
Faculty of Medicine, University of Oslo, 0407 Oslo, Norway

Y. Shima · K. Kitaoka · K. Tomita
Department of Orthopedic Surgery, Kanazawa University,
13-1 Takaramachi, Kanazawa 920-8641, Japan

Introduction

Stress fractures are a major problem for athletic and military populations. Hame et al. [28] found a stress fracture incidence of 1.4% in collegiate athletes over a 15-year observation period. Moreover, the incidence of stress fractures among infantry units of the Finnish Army was 8.4% [78], while the incidence of stress fractures among Israeli elite infantry recruits over 14 weeks of basic training was 16–25%, as diagnosed by scintigraphy on the basis of clinical suspicion [48].

A slow healing process may interrupt participation in physical activity for a relatively long time period. Also, conservative treatment does not always lead to healing and may result in delayed union or nonunion. In certain circumstances, surgical treatment may allow a quicker return to activity, but the healing process cannot readily be accelerated. Consequently, there is interest in developing an effective pharmacologic intervention to either prevent stress fractures or accelerate recovery after a stress fracture occurs. Until recently, pharmaceutical agents were prescribed only for the treatment of inflammation and pain rather than to promote more rapid healing of stress fractures.

Although the pathogenesis of stress fractures is not fully understood, development of such a fracture likely represents a failure of functional adaptation [8, 18]. Accumulation of microdamage from repetitive loading of a bone (fatigue failure) leads to crack initiation. This is the first step in the pathogenesis of a stress fracture. If such an initial process is inadequately repaired, it can lead to crack propagation [59]. Stress fractures in athletes and military recruits are the result of either fatigue failure secondary to high strains or strain rates, or mediated through a bone remodeling response whereby the bone attempts to

Published online: 02 December 2008

strengthen itself when subjected to high strains or strain rates, or new strain patterns. Milgrom et al. [49] have shown in their in vivo human bone strain gauge study that tibial stress fractures are likely due to bone remodeling, while metatarsal stress fractures are caused by cyclic overloading alone.

Over the past decade, bisphosphonates have been widely used to treat a variety of bone diseases and have been shown to increase bone mass and decrease fracture risk in postmenopausal, osteoporotic women. The marked inhibitory action of bisphosphonates on osteoclast-mediated bone resorption has also led to successful treatment of pathologic processes associated with increased bone remodeling such as Paget's disease, bone tumors, and metastases. Given their inhibitory action on osteoclast activity, short-term suppression of bone remodeling using bisphosphonates could prevent the initial bone loss observed during the remodeling response to high bone strains and potentially prevent stress fractures [19]. This concept is not new. Physicians have empirically treated athletes who suffer from stress fractures with bisphosphonates, but this is controversial and has not been well investigated [3, 24].

The present review summarizes and discusses the current understanding and the potential role of bisphosphonates for the treatment and prevention of stress fractures in athletes.

Pathogenesis of stress fractures and the relationship to bisphosphonates

As stated above, stress fractures occur when a bone fails to remodel adequately following the application of repetitive sub-threshold stress. The first stage of bone remodeling involves bone resorption, which further weakens the already compromised bone [19]. A mathematical model proposes that the porosity introduced by remodeling contributes to an unstable situation in which a stress fracture will occur [44]. Experimental studies with a rabbit impulsive loading model [17] also suggested that a positive feedback between loading and remodeling might be a feature of stress fracture pathogenesis. By 6 weeks of loading, activation of new bone remodeling had increased further still and there was a tenfold increase in bone microdamage. The incidence of overt stress fractures in these animals had increased to 68% after 6 weeks. These data suggest that overloading first creates a biological remodeling response, which is associated with the early signs of a stress fracture. Continued loading causes acceleration of bone microdamage accumulation, which further increases the incidence of stress fractures, perhaps through a positive feedback mechanism [19]. Taken together, these experiments have suggested that the suppression of bone remodeling, which prevents the increased porosity associated with remodeling and maintains lower strains on the bone, can prevent stress fractures.

One would expect that an increase in bone remodeling would be accompanied by an elevation of serum or urine biochemical markers that reflect the remodeling process. In their prospective study, Murguia et al. [53] detected a significant increase in plasma hydroxyproline during the first week of military training in a group of recruits who subsequently presented with stress fractures, compared to those who did not. This showed that an initially higher bone remodeling rate is a risk factor for subsequent stress fractures. According to this result, preventive bisphosphonate treatment may be feasible for those who have increased bone remodeling at baseline. However, Bennell et al. [8] reported that bone remodeling in athletes who developed stress fractures was not different from those who did not develop stress fractures at baseline, or immediately prior or subsequent to the start of bone pain. The results from military recruits may not generalize to athletes as they represent a different population. Failure to detect increased bone remodeling, either prior to or following the onset of stress fractures in athletes, may reflect overall total body bone remodeling and the tests may not be sufficiently sensitive enough to detect locally accelerated bone remodeling.

Effect of bisphosphonates on fracture healing

Over the years, there have been concerns about whether or not bisphosphonates interfere with the fracture healing. Because they suppress bone remodeling, one might expect that bisphosphonates interfere with fracture repair. Li et al. [37] have reported in a growing rat model using incadronate that bisphosphonate treatment resulted in a larger fracture callus and delayed maturation of the fracture. Alendronate treatment also suppressed remodeling of the fracture callus in ovariectomized rats [20]. These changes may be secondary to inhibition of bone resorption because bone formation and resorption are intimately linked. Conversely, there are reassuring reports on this topic that show fracture callus remodeling is not a problem in several animal models unless very high doses of bisphosphonates are used [7, 25].

In contrast to these concerns, there are now several reports suggesting that bisphosphonates may actually enhance fracture repair, probably by stabilizing the fracture callus [42]. Other studies relevant to this problem include the improved osseointegration of metal implants in ovariectomized rats treated with ibandronate [34]. There are also potential applications of bisphosphonates in orthopedics, including improved healing in distraction osteogenesis [39,

40], which conserves bone architecture after osteonecrosis [35, 41, 60].

The process of bone and fracture repair consists of an anabolic (bone forming) response and a catabolic (bone resorbing) response. In the absence of an anabolic response, anti-catabolic treatment alone does not lead to union in a rat femoral critical defect model [42]. Bisphosphonate treatment may require anabolic conjunctive therapy to ensure enhanced successful repair [16, 42], but this cannot be directly applied to the treatment of stress fractures as they represent different features. Bisphosphonates as anti-catabolic agents would be considered satisfactory for the treatment of stress fractures, assuming that most athletes with stress fractures, except in some special situations, e.g., female athlete triad have a normal anabolic bone homeostatic response. However, if systemic bone morphogenetic proteins are available as anabolic agents, using them in combination with bisphosphonates [42] may be more efficacious for the treatment of stress fractures.

In recent years, dosing regimens used for treating osteoporosis have evolved such that the time between doses has increased. From routine daily therapy, oral therapy is now standardized to weekly dosing for alendronate and risedronate and monthly dosing for ibandronate. Recent osteoporosis trials support the use of intravenous ibandronate at 3 month intervals, and zoledronic acid (ZA) as a once-yearly infusion [12, 21]. Previous preclinical studies using continuous bisphosphonate therapy may not be, therefore, relevant to such intermittent dosing regimens [5]. A single systemic dose of pamidronate administered at the time of fracture increased bone mineral content (BMC), volume, and strength of united fractures [4]. There were further increases in bone volume and strength when the dose of zoledronic acid was delayed by 2 weeks in a rat femoral critical defect model [42]. Amanat et al. [5] recently reported that delaying the single dose systemic zoledronic acid administration to 1 or 2 weeks after the occurrence of the fracture increased callus volume, callus BMC, and mechanical strength in a rat fracture model.

Bisphosphonates are well known to reduce pain in a wide variety of underlying bone conditions, such as osteolytic metastasis, multiple myeloma, and localized transient osteoporosis (LTO; bone marrow edema syndrome) [61, 62]. Increased bone remodeling and low bone mineral density (BMD) indicate a potential role for bisphosphonate therapy in LTO. Miltner et al. [51] reported a case of transient osteoporosis of the navicular bone in a 400 m sprinter and the successful treatment with alendronate. This relief of bone pain is mediated not only through the inhibition of osteoclast function, but also through an inhibition of cytokine production by macrophages and prostaglandin synthesis by a variety of cells [23].

Recently, extracorporeal shock wave therapy was shown to be an effective method to treat intractable stress fractures in athletes [72]. Shock wave therapy induces angiogenesis-related growth factors and stimulates neovascularization, which improves blood supply and increases cell proliferation at the fracture site. Hausman et al. [29] showed that angiogenesis is essential to the very early stages of fracture healing, and suggested that impairment of fracture healing may be an adverse effect of clinical treatments with anti-angiogenic drugs. Considering the anti-angiogenic properties [26, 65, 83], administration of nitrogen-containing bisphosphonates at the initial stage of fracture healing may have an adverse effect on stress fracture treatment.

Bisphosphonates and fatigue loading

In a short-term alendronate treatment study in rats [6], resorption space density was suppressed in the adapted groups receiving alendronate treatment. The lowest resorption space density values were found in the adapted groups that were pretreated with alendronate. However, work-to-failure was significantly improved in the adapted groups with post-treatment but not in the pre-treatment group. Therefore, pre-treatment with alendronate had a less advantageous effect on adaptation to fatigue when compared with post-treatment. In addition, the authors suggested that a treatment period of 14 days was too short to have any significant effect of alendronate on skeletal remodeling during functional adaptation. During post-fatigue treatment, inhibition of osteoclastic remodeling by alendronate may have been reduced by physiological stress [6]. In mice receiving both glucocorticoid and alendronate concomitantly, the expected apoptotic effect of bisphosphonates on osteoclasts was reduced [80].

Over-suppression and microdamage accumulation

Concerns have been raised about potential over-suppression of bone remodeling during long-term use of bisphosphonates. Although the administration of bisphosphonates for athletes would be a relatively short-term treatment, physicians should at least know about the long-term risks. After bone uptake, bisphosphonates are liberated again only when the bone in which they are deposited is resorbed. Thus, the half-life of bisphosphonates in bone is very long, ranging from 1 to 10 years among different species, and is dependent largely on the rate of bone remodeling [38]. There appears to be no progression of the anti-resorptive effect with time even when the compounds are given continuously, which suggests that bisphosphonate buried in the

bone is inactive, at least as long as it remains sequestered there [63]. In dog ribs treated with risedronate or alendronate for 1 year, alendronate has been shown to inhibit normal microdamage repair that arises from a marked suppression of bone remodeling, which in turn results in accumulation of microdamage [2, 37, 46, 47]. Bone remodeling decreased 53 and 68% as a result of risedronate or alendronate treatments, while the corresponding increase in microcrack damage was 490 and 630%, respectively. In addition, the energy required to fracture the rib was significantly decreased by 19% in the alendronate treatment group. While these experiments used bisphophonate doses several times higher than the equivalent doses for human osteoporosis patients, it strongly suggests that bone remodeling is necessary to prevent fatigue microdamage from accumulating and weakening the bone.

Long-term use (5–10 years) of bisphosphonates for osteoporosis therapy appears to be safe [11, 15]. However, there is a case series [55] that revealed severe deficiencies in bone formation in nine patients on long-term alendronate therapy (3–8 years). This resulted in an increased susceptibility to non-spinal fractures that healed poorly. In addition, Ott [55] speculated that long-term alendronate treatment in humans might impair mechanical bone strength. This suggestion was based on the apparent increase in the rate of vertebral fractures with prolonged treatment [75], though refuted by the authors of that report [76]. The induction of osteopetrotic-like lesions in a child treated with extremely high doses of pamidronate has also been reported [81]. Lenart et al. [36] recently showed that low-energy fractures of the femoral shaft with a simple, transverse pattern and hypertrophy of the diaphyseal cortex were associated with alendronate use. They suggested that this may result from propagation of stress fractures whose repair was retarded by diminished osteoclast activity and impaired microdamage repair resulting from prolonged use. Long-term suppression of bone remodeling by bisphosphonate also increased non-enzymatic cross-linking and could result in brittle bones [64, 68].

Potential adverse effects

It is always necessary to consider the risks and benefits of any prescribed medication. When treating a non-life threatening disease such as stress fractures, off-label use of a drug demands special caution. In a case series using intravenous pamidronate for the treatment of stress fractures, the most common short-term side effects were nausea, fatigue, arthralgias, and myalgias [71]. All of the side effects resolved within 24–48 h. Since nausea was the main problem with the 90 mg dose when compared with the 60 mg dose, the authors recommended using a 60 mg treatment dose. On the other hand, in a randomized controlled study of military recruits, risedronate use for the prevention of stress fractures had no more side effects than a placebo treatment [50].

Oral bisphosphonates can result in stomach upset, inflammation, and erosions of the esophagus, which is the main problem of all oral nitrogen-containing preparations. This can be prevented by remaining seated upright for 30–60 min after taking the medication. A number of cases of severe bone, joint, or musculoskeletal pain associated with oral bisphosphonates, alendronate and risedronate, have been reported [84]. These symptoms improved after discontinuation of the drug treatment. Intravenous nitrogen-containing bisphosphonates can give undesirable inflammatory reactions, including an increase in acute-phase proteins, fever, flu-like symptoms, and ophthalmic inflammation, after the first infusion [1, 43, 69, 73]. These are thought to occur because of their potential to activate human γ,δ-T cells [74]. Notably, these symptoms do not recur with subsequent infusions. Some of the intravenous bisphosphonates, in particular zoledronic acid, have nephrotoxic potential [14, 30].

Recently, another potential complication of these agents has surfaced. Osteonecrosis of the jaw (ONJ) occurred in multiple myeloma or metastatic cancer patients treated with intravenous bisphosphonates [10, 45, 67]. These reports have led to a growing concern about the safety of oral bisphosphonates in patients with osteoporosis. In a literature review, Pazianas et al. [58] identified 26 cases of ONJ in patients receiving oral bisphosphonates. Considering that millions of patients have been prescribed bisphosphonates for the treatment of osteoporosis, this prevalence of ONJ was relatively low. The mandible was more commonly affected than the maxilla (2:1 ratio), and 60% of cases were preceded by a dental surgical procedure [82]. The most common characteristics of those who developed ONJ were an age $\geq$60 years (only one patient was aged <40 years), female sex, and patients that had received previous invasive dental treatment [58]. At present, there is insufficient data available to construct evidence-based guidelines for the prevention and therapy of ONJ. In the case of administration of bisphosphonates to athletes, a physician should check their previous dental history and current dental condition, and inform the patients about the low risk of developing ONJ, irrespective of the route and frequency of bisphosphonate administration.

Because of increased sports participation in children and adolescents, athletes with open physis are predisposed to stress fractures. There are some concerns about the impact of bisphosphonates on open physis, chondro-osseous modeling, and consequent growth in otherwise normal long bones. Smith et al. [70] showed that nitrogen-containing

bisphosphonates can cause transient effects on physeal cell morphology and retention of cartilaginous matrix, which coincides with a growth disturbance (3% decrease in final long bone length), even in a short-term 6-week growing animal model. On the other hand, in a radiographic quantification study, Ward et al. [79] showed that clinically relevant doses of bisphosphonates did not necessarily disturb physeal modeling in the distal femur throughout childhood. In a case series by van Persijn van Meerten [77], bisphosphonate treatment in children with open physis characteristically resulted in epi- and metaphyseal sclerosis, but this was a reversible phenomenon. However, so far there is a lack of evidence about the safe use of bisphosphonates for adolescent athletes with open physis.

Although the pharmacologic activities of bisphosphonates are retained for a period of time after cessation of treatment, the effects of bisphosphonates are likely transient and may disappear once the drug is withdrawn. Therefore, short-term exposure to bisphosphonates for the treatment of stress fractures would not be expected to cause long-term deleterious effects on the skeleton [19].

The safety of bisphosphonates in women who are pregnant, or are of childbearing age, also has not been clearly established. In rat studies, alendronate was found to cross the placenta and accumulate in fetal bone [57], where the presence of alendronate may interfere with fetal bone mineralization and development. The half-life of bisphosphonates is proportional to bone remodeling time, which may be over 1 year in rats [52]. Therefore, it may take several years for a young woman to completely clear the drug from her body. Any harmful effects on the fetus could potentially persist for years after the initial treatment. However, there have been no case reports to date of teratogenic effects in humans.

Clinical intervention using bisphosphonates for stress fractures

To date, there have been no randomized controlled studies about bisphosphonate treatment after stress fractures. However, a case series [71] recently reported the successful use of intravenous pamidronate in five intercollegiate female athletes with tibial stress fractures. The five subjects showed bone scan results consistent with stress fractures, with four of five athletes acquiring symptoms more than 5 months before treatment. A 30 mg test dose of pamidronate was given intravenously over 2 h, followed by four additional treatments at weekly intervals in 60 or 90 mg amounts. With the initial treatment, four of five subjects were able to continue training without symptoms within 72 h. Only one patient missed 3 weeks of training. The symptoms resolved in all five athletes within a few weeks of treatment and all remained asymptomatic at a minimum of 49 months of follow-up. Although no decision regarding the efficacy of bisphosphonates in stress fracture treatment can be made from this uncontrolled study with a small population, these investigators believe that the treatment is promising and plan to do a prospective study.

There has been only one randomized controlled study concerning the prevention of stress fractures using oral bisphosphonate. Milgrom et al. [50] conducted a study of 324 male Israeli military recruits using 30 mg risedronate, or a placebo, daily for 10 days during the first 2 weeks of basic training, before they started any physically demanding training. After the initial 10-day loading dose, subjects received a 30 mg maintenance dose of risedronate, once a week for the next 12 weeks of the remaining 13-week training period. The primary outcome measure was the occurrence of a stress fracture during the study period. Over one-third of the entire study group discontinued treatment because of concerns regarding potential adverse side effects, although only two soldiers actually reported symptoms. Despite the early dropout rate, intention-to-treat analysis and per-protocol analysis showed risedronate did not lower the incidence of stress fractures. Instead, the incidence of fatigue or stress fractures in the distal limb (tibia and metatarsus) was higher in subjects that received risedronate therapy before the period of strenuous activity, although this finding was not statistically significant. This observation fits with the rat model data from Barrett et al. [6]. They suggested that short-term pre-emptive treatment with alendronate did not protect bone from fatigue injury in a rat ulna cyclic fatigue loading model. Further research is warranted regarding stress fracture prevention in both military and athletic populations.

Discussion

Given the pathogenesis of stress fractures, there is reason to consider the potential role of bisphosphonates for the treatment of stress fractures based on limited information. However, no solid evidence-based interventions to prevent lower extremity stress reactions or fractures has existed so far [66]. Moreover, the present review confirmed that there is no conclusive evidence to prove any effect of bisphosphonates on stress fracture healing in humans.

Whenever we consider a treatment plan for stress fractures, we must understand why the injury has occurred in the first place. A dynamic balance exists between the accumulation of microdamage and the host repair processes. Any intrinsic and extrinsic factors that disrupt this dynamic balance can increase the risk of stress fracture. Intrinsic factors include metabolic state, menstrual patterns, level of fitness, muscle endurance, anatomic alignment, and bone

vascularity [27, 33]. Extrinsic factors include training regimens, nutritional or dietary habits, and playing equipment (footwear, playing surface, etc.). Understanding these underlying causes are essential before any treatment of stress fractures is started.

It is estimated that >50% of a dose of intravenous bisphosphonate is bioavailable for incorporation into the bone matrix, compared with <1% of oral bisphosphonate [9, 22]. Intravenous bisphosphonates have improved bioavailability and do not produce the gastrointestinal side effects that oral bisphosphonates do; however, there are some possibilities of non-trivial side effects. Intravenous administration of clodronate and pamidronate require slow, prolonged infusion to avoid renal toxicity [13] and therefore must be undertaken in a hospital setting. This is inconvenient, labor-intensive, and costly and can be associated with complications [56]. Because they are self-administered, oral bisphosphonates provide some practical advantages. In either case, less frequently administered dosage regimens may enhance compliance with bisphosphonate treatment. Because of the relatively short-term administration of bisphosphonates and enthusiasm for the treatment of stress fractures, the route of administration may present no problems for athletes.

Dosage and administration period of bisphosphonates for the treatment of stress fractures remain unsettled issues. Even at a higher dose than that used to treat human osteoporosis patients, any significant effect of oral bisphosphonates on skeletal modeling during functional adaptation would possibly require a longer treatment period than 14 days, either before or after bone fatigue [6, 50]. In administration of intravenous bisphosphonates, clinically relevant doses would likely suffice for the treatment of stress fractures [71]. It is noteworthy that the use of intravenous bisphosphonates during the acute phase of stress fractures allowed athletes to continue sports participation without pain or restrictions, even though the results were from a small population without a control group.

In a rat fracture [5] or bone defect model [42], a single systemic dose and delayed administration of intravenous bisphosphonate, 1 or 2 weeks after making the fractures or defects, was found to be more effective. It is possible that by waiting until bone repair had commenced, the effective dose reaching the repair site may have increased because of greater availability of target mineral binding sites. Alternatively, the delay may have allowed the anabolic response to gather pace before administration of bisphosphonates. Conversely, an animal study [6] and clinical study [50] suggested brief pre-emptive treatment with alendronate before fatigue loading did not protect the skeleton from stress injuries. Because stress fractures do not occur in acute onset and bone has already commenced the repair process at the time of treatment, it is not necessary to delay the administration of bisphosphonates for the treatment of stress fractures in athletes.

Oral bisphosphonate appears to have few side effects and no associated mortality. However, considering the generally healthy nature of athletes, it seems unlikely that short-term and clinically relevant doses of intravenous bisphosphonate treatment will cause more severe side effects than that of oral bisphosphonate treatment. If high doses of oral bisphosphonates are used to compensate for their low bioavailability, it may cause more problems in view of safety. For adolescents with open physis and women who are of childbearing age, the safety use of bisphosphonates has not yet established. Therefore, current studies of the use of bisphosphonates in young athletes should be limited to men without open physis. If it is found to be efficacious in the treatment of stress fractures, further studies in women, along with post-treatment surveillance for the occurrence of birth defects, should be initiated [32].

The question remains as to what kind of bisphosphonates should be used for the treatment of stress fractures. This seems likely because there is no theoretical basis for other bisphosphonates to behave differently. Furthermore, when not given in excess, many bisphosphonates have a positive effect on the mechanical properties of bone. However, further investigations are required to compare the different type of bisphosphonates regarding the effectiveness and safety in the treatment of stress fractures.

Unfortunately, stress fractures occur with varying grades and locations. The relatively low number of each combination of grade and location seen at one clinical site makes prospective controlled studies difficult [31]. The proper role of bisphosphonates in stress fracture treatment can be determined only by a well-designed clinical trial with groups randomized according to gender, fracture site, MRI findings, and activity.

Conclusions

Given the inhibitory action on osteoclast-mediated bone resorption, short-term suppression of bone remodeling using bisphosphonates could potentially treat stress fractures, for example, tibial stress fractures that are likely to be remodeling-mediated, and therefore prevent stress fractures becoming regular fractures. However, there is still no conclusive evidence to prove any effect of bisphosphonates on stress fracture healing in humans. Until the results of well-designed clinical trials are available, it is prudent to limit the use of bisphosphonates in the treatment of stress fractures.

References

1. Adami S, Bhalla AK, Dorizzi R, Montesanti F, Rosini S, Salvagno G, Lo Cascio V (1987) The acute-phase response after bisphosphonate administration. Calcif Tissue Int 41:326–331
2. Ali SM, Esteva FJ, Hortobagyi G, Harvey H, Seaman J, Knight R, Costa L, Lipton A (2001) Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. J Clin Oncol 19:3434–3437
3. Allen MR, Iwata K, Phipps R, Burr DB (2006) Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. Bone 39:872–879
4. Amanat N, Brown R, Bilston LE, Little DG (2005) A single systemic dose of pamidronate improves bone mineral content and accelerates restoration of strength in a rat model of fracture repair. J Orthop Res 23:1029–1034
5. Amanat N, McDonald M, Godfrey C, Bilston L, Little D (2007) Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. J Bone Miner Res 22:867–876
6. Barrett JG, Sample SJ, McCarthy J, Kalscheur VL, Muir P, Prokuski L (2007) Effect of short-term treatment with alendronate on ulnar bone adaptation to cyclic fatigue loading in rats. J Orthop Res 25:1070–1077
7. Bauss F, Schenk RK, Hört S, Müller-Beckmann B, Sponer G (2004) New model for simulation of fracture repair in full-grown beagle dogs: model characterization and results from a long-term study with ibandronate. J Pharmacol Toxicol Methods 50:25–34
8. Bennell KL, Malcolm SA, Brukner PD, Green RM, Hopper JL, Wark JD, Ebeling PR (1998) A 12-month prospective study of the relationship between stress fractures and bone turnover in athletes. Calcif Tissue Int 63:80–85
9. Berenson JR, Rosen L, Vescio R, Lau HS, Woo M, Sioufi A, Kowalski MO, Knight RD, Seaman JJ (1997) Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. J Clin Pharmacol 37:285–290
10. Bilezikian JP (2006) Osteonecrosis of the jaw—do bisphosphonates pose a risk? N Engl J Med 355:2278–2281
11. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR, FLEX Research Group (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the fracture intervention trial long-term extension (FLEX): a randomized trial. JAMA 296:2927–2938
12. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR, HORIZON Pivotal Fracture Trial (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 356:1809–1822
13. Body JJ, Mancini I (2002) Bisphosphonates for cancer patients: why, how, and when? Support Care Cancer 10:399–407
14. Body JJ (2005) Bisphosphonates in metastatic bone disease: renal safety matters. Oncologist 10:1–2
15. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA, Alendronate Phase III Osteoporosis Treatment Study Group (2004) Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189–1199
16. Bransford R, Goergens E, Briody J, Amanat N, Cree A, Little D (2007) Effect of zoledronic acid in an L6–L7 rabbit spine fusion model. Eur Spine J 16:557–562
17. Burr DB, Milgrom C, Boyd RD, Higgins WL, Robin G, Radin EL (1990) Experimental stress fractures of the tibia. Biological and mechanical aetiology in rabbits. J Bone Joint Surg Br 72:370–375
18. Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH (1997) Bone microdamage and skeletal fragility in osteoporotic and stress fractures. J Bone Miner Res 12:6–15
19. Burr DB (2001) Pharmaceutical treatments that may prevent or delay the onset of stress fractures. In: Burr DB, Milgrom C (eds) Muscloskeletal fatigue and stress fractures. CRC Press, Boca Raton, pp 259–270
20. Cao Y, Mori S, Mashiba T, Westmore MS, Ma L, Sato M, Akiyama T, Shi L, Komatsubara S, Miyamoto K, Norimatsu H (2002) Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. J Bone Miner Res 17:2237–2246
21. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, Reginster JY, Zaidi M, Felsenberg D, Hughes C, Mairon N, Masanauskaite D, Reid DM, Delmas PD, Recker RR (2008) Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA Study. J Rheumatol 35:488–497
22. Ezra A, Golomb G (2000) Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. Adv Drug Deliv Rev 42:175–195
23. Felix R, Bettex JD, Fleisch H (1981) Effect of diphosphonates on the synthesis of prostaglandins in cultured calvaria cells. Calcif Tissue Int 33:549–552
24. Flinn SD (2002) Changes in stress fracture distribution and current treatment. Curr Sports Med Rep 1:272–277
25. Flora L, Hassing GS, Cloyd GG, Bevan JA, Parfitt AM, Villanueva AR (1981) The long-term skeletal effects of EHDP in dogs. Metab Bone Dis Relat Res 3:289–300
26. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, Clézardin P (2002) Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 62:6538–6544
27. Gehrmann RM, Renard RL (2006) Current concepts review: Stress fractures of the foot. Foot Ankle Int 27:750–757
28. Hame SL, LaFemina JM, McAllister DR, Schaadt GW, Dorey FJ (2004) Fractures in the collegiate athlete. Am J Sports Med 32:446–451
29. Hausman MR, Schaffler MB, Majeska RJ (2001) Prevention of fracture healing in rats by an inhibitor of angiogenesis. Bone 29:560–564
30. Jackson G (2005) Safety and compliance of intravenous and oral dosing regimens. Oncologist 10:313–314
31. Kaeding CC (2006) Stress fractures. Clin Sports Med 25:15–16
32. Koester MC, Spindler KP (2006) Pharmacologic agents in fracture healing. Clin Sports Med 25:63–73
33. Korpelainen R, Orava S, Karpakka J, Siira P, Hulkko A (2001) Risk factors for recurrent stress fractures in athletes. Am J Sports Med 29:304–310
34. Kurth AH, Eberhardt C, Müller S, Steinacker M, Schwarz M, Bauss F (2005) The bisphosphonate ibandronate improves implant integration in osteopenic ovariectomized rats. Bone 37:204–210
35. Lai KA, Shen WJ, Yang CY, Shao CJ, Hsu JT, Lin RM (2005) 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 87:2155–2159
36. Lenart BA, Lorich DG, Lane JM (2008) Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med 358:1304–1306
37. Li C, Mori S, Li J, Kaji Y, Akiyama T, Kawanishi J, Norimatsu H (2001) Long-term effect of incadronate disodium (YM–175) on

fracture healing of femoral shaft in growing rats. J Bone Miner Res 16:429–436
38. Lin JH (1996) Bisphosphonates: a review of their pharmacokinetic properties. Bone 18:75–85
39. Little DG, Cornell MS, Hile MS, Briody J, Cowell CT, Bilston L (2001) Effect of pamidronate on distraction osteogenesis and fixator-related osteoporosis. Injury 32:SD14–SD20
40. Little DG, Smith NC, Williams PR, Briody JN, Bilston LE, Smith EJ, Gardiner EM, Cowell CT (2003) Zoledronic acid prevents osteopenia and increases bone strength in a rabbit model of distraction osteogenesis. J Bone Miner Res 18:1300–1307
41. Little DG, Peat RA, Mcevoy A, Williams PR, Smith EJ, Baldock PA (2003) Zoledronic acid treatment results in retention of femoral head structure after traumatic osteonecrosis in young Wistar rats. J Bone Miner Res 18:2016–2022
42. Little DG, McDonald M, Bransford R, Godfrey CB, Amanat N (2005) Manipulation of the anabolic and catabolic responses with OP-1 and zoledronic acid in a rat critical defect model. J Bone Miner Res 20:2044–2052
43. Macarol V, Fraunfelder FT (1994) Pamidronate disodium and possible ocular adverse drug reactions. Am J Ophthalmol 118:220–224
44. Martin B (1995) Mathematical model for repair of fatigue damage and stress fracture in osteonal bone. J Orthop Res 13:309–316
45. Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 61:1115–1117
46. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB (2000) Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 15:613–620
47. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB (2001) Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. Bone 28:524–531
48. Milgrom C, Simkin A, Eldad A, Nyska M, Finestone A (2000) Using bone's adaptation ability to lower the incidence of stress fractures. Am J Sports Med 28:245–251
49. Milgrom C, Finestone A, Sharkey N, Hamel A, Mandes V, Burr D, Arndt A, Ekenman I (2002) Metatarsal strains are sufficient to cause fatigue fracture during cyclic overloading. Foot Ankle Int 23:230–235
50. Milgrom C, Finestone A, Novack V, Pereg D, Goldich Y, Kreiss Y, Zimlichman E, Kaufman S, Liebergall M, Burr D et al (2004) The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone 35:418–424
51. Miltner O, Niedhart C, Piroth W, Weber M, Siebert CH (2003) Transient osteoporosis of the navicular bone in a runner. Arch Orthop Trauma Surg 123:505–508
52. Minsker DH, Manson JM, Peter CP (1993) Effects of the bisphosphonate, alendronate, on parturition in the rat. Toxicol Appl Pharmacol 121:217–223
53. Murguia MJ, Vailas A, Mandelbaum B, Norton J, Hodgdon J, Goforth H, Riedy M (1988) Elevated plasma hydroxyproline. A possible risk factor associated with connective tissue injuries during overuse. Am J Sports Med 16:660–664
54. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY (2005) Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 90:1294–1301
55. Ott SM (2001) Fractures after long-term alendronate therapy. J Clin Endocrinol Metab 86:1835–1836
56. Parker L (1999) I.v. devices and related infections: causes and complications. Br J Nurs 8:1491–1498
57. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A (1999) Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 60:68–73
58. Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P (2007) A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. Clin Ther 29:1548–1558
59. Pepper M, Akuthota V, McCarty EC (2006) The pathophysiology of stress fractures. Clin Sports Med 25:1–16
60. Ramachandran M, Ward K, Brown RR, Munns CF, Cowell CT, Little DG (2007) Intravenous BP therapy for traumatic osteonecrosis of the femoral head in adolescents. J Bone Joint Surg Am 89:1727–1734
61. Ringe JD, Dorst A, Faber H (2005) Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate. Osteoporos Int 16:2063–2068
62. Ringe JD, Body JJ (2007) A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover. Clin Exp Rheumatol 25:766–774
63. Russell RG, Watts NB, Ebetino FH, Rogers MJ (2008) Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 19:733–759
64. Saito M, Mori S, Mashiba T, Komatsubara S, Marumo K (2008) Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs. Osteoporos Int 19:1343–1354
65. Santini D, Vincenzi B, Galluzzo S, Battistoni F, Rocci L, Venditti O, Schiavon G, Angeletti S, Uzzalli F, Caraglia M, Dicuonzo G, Tonini G (2007) Repeated intermittent low-dose therapy with zoledronic acid induces an early, sustained, and long-lasting decrease of peripheral vascular endothelial growth factor levels in cancer patients. Clin Cancer Res 13:4482–4486
66. Shaffer SW, Uhl TL (2006) Preventing and treating lower extremity stress reactions and fractures in adults. J Athl Train 41:466–469
67. Shane E, Goldring S, Christakos S, Drezner M, Eisman J, Silverman S, Pendrys D (2006) Osteonecrosis of the jaw: more research needed. J Bone Miner Res 21:1503–1505
68. Siegmund T, Allen MR, Burr DB (2008) Failure of mineralized collagen fibrils: modeling the role of collagen cross-linking. J Biomech 41:1427–1435
69. Siris ES (1993) Bisphosphonates and iritis. Lancet 341:436–437
70. Smith EJ, Little DG, Briody JN, McEvoy A, Smith NC, Eisman JA, Gardiner EM (2005) Transient disturbance in physeal morphology is associated with long-term effects of nitrogen-containing bisphosphonates in growing rabbits. J Bone Miner Res 20:1731–1741
71. Stewart GW, Brunet ME, Manning MR, Davis FA (2005) Treatment of stress fractures in athletes with intravenous pamidronate. Clin J Sport Med 15:92–94
72. Taki M, Iwata O, Shiono M, Kimura M, Takagishi K (2007) Extracorporeal shock wave therapy for resistant stress fracture in athletes: a report of 5 cases. Am J Sports Med 35:1188–1192
73. Thiébaud D, Sauty A, Burckhardt P, Leuenberger P, Sitzler L, Green JR, Kandra A, Zieschang J, Ibarra de Palacios P (1997) An in vitro and in vivo study of cytokines in the acute-phase response associated with bisphosphonates. Calcif Tissue Int 61:386–392
74. Thompson K, Rogers MJ (2004) Statins prevent bisphosphonate-induced gamma, delta-T-cell proliferation and activation in vitro. J Bone Miner Res 19:278–288
75. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, Bone HG, Santora AC, Wu M, Desai R, Ross PD (2000) Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III

Osteoporosis Treatment Study Group. J Clin Endocrinol Metab 85:3109–3115
76. Tonino RP (2001) Safety of long-term alendronate. J Clin Endocrinol Metab 86:1835–1836
77. van Meerten EL, Kroon HM, Papapoulos SE (1992) Epi- and metaphyseal changes in children caused by administration of bisphophonates. Radiology 184:249–254
78. Ward K, Cowell CT, Little DG (2005) Quantification of metaphyseal modeling in children treated with bisphosphonates. Bone 36:999–1002
79. Välimäki VV, Alfthan H, Lehmuskallio E, Löyttyniemi E, Sahi T, Suominen H, Välimäki MJ (2005) Risk factors for clinical stress fractures in male military recruits: a prospective cohort study. Bone 37:267–273
80. Weinstein RS, Chen JR, Powers CC, Stewart SA, Landes RD, Bellido T, Jilka RL, Parfitt AM, Manolagas SC (2002) Promotion of osteoclast survival and antagonism of bisphosphonate-induced osteoclast apoptosis by glucocorticoids. J Clin Invest 109:1041–1048
81. Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S (2003) Bisphosphonate-induced osteopetrosis. N Engl J Med 349:457–463
82. Woo SB, Hellstein JW, Kalmar JR (2006) Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 144:753–761
83. Wood J, Bonjean K, Ruetz S, Bellahcène A, Devy L, Foidart JM, Castronovo V, Green JR (2002) Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 302:1055–1061
84. Wysowski DK, Chang J (2005) Alendronate and risedronate: reports of severe bone, joint, and muscle pain. Arch Intern Med 165:346–347