Title

Use of Bisphosphonates for the Treatment of Stress Fractures in Athletes

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Abstract

A literature review was performed to investigate the potential role of bisphosphonates (BPs) for the treatment of stress fractures in athletes. Given the inhibitory action on osteoclast-mediated bone resorption, short-term suppression of bone remodeling using BPs could potentially treat stress fractures and prevent stress fractures to become regular fractures. To date, while there are some animal studies showing the scientific basis of BPs on stress fractures, we must say that there is still no conclusive evidence to prove any effect of BPs 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 BPs for the treatment of stress fractures.

Key words

Bisphosphonates, treatment, stress fracture, microdamage, bone remodeling

Introduction

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

The slow healing process may interrupt participation in physical activity for a relatively long time. Conservative treatment does not always lead to healing, resulting 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 the recovery from a stress fracture. Until recently, pharmaceutical agents have been prescribed only for the treatment of inflammation and pain rather than to promote more rapid healing of stress fracture.

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 bone (fatigue failure) leads to crack initiation

as the first step in the pathogenesis of 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 bone remodeling response by attempting to 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 to be remodeling mediated while metatarsal stress fractures are caused by cyclic overloading alone.

Over the past decade, bisphosphonates (BPs) have been widely used to treat a variety of bone disease and has been shown to increase bone mass and decrease fracture risk in postmenopausal, osteoporotic women. The marked inhibitory action of BPs on osteoclast-mediated bone resorption has also led to success in the treatment of pathologic processes 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 BPs could prevent the initial loss of bone during the remodeling response to high bone strains and potentially prevent stress fracture [19]. This concept is not new. Physicians have empirically treated athletes who suffer from stress fracture with BPs, but these are controversial and little investigated [3, 24].

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

Pathogenesis of stress fractures and its relation to usefulness of bisphosphonates

As stated above, a stress fracture occurs essentially when bone fails to remodel adequately with the application of repetitive subthreshold stress. The first stage of bone remodeling involves bone resorption, further weakening the already compromised bone [19]. A mathematical model [44] has shown that porosity introduced by remodeling can contribute via a positive feedback mechanism to an unstable situation in which a stress fracture will occur. Experimental studies with the rabbit impulsive loading model [17] also suggested that positive feedback between loading and remodeling might be a feature of the pathogenesis of stress fractures. By 6 weeks of loading, activation of new bone remodeling had increased further still, and bone microdamage was increased by more than 10 times. The incidence of overt stress fractures in these animals had increased to 68% after 6 weeks. These data suggested that overloading first creates a biological remodeling response, which can be associated with early signs of a stress fracture, and that continued loading will cause acceleration of bone microdamage

accumulation that will further increase the incidence of stress fracture, perhaps through a positive feedback [19]. Taken together, these experiments have suggested that 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 reflective of remodeling. 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 a stress fracture, compared to those who did not. This showed that an initially higher bone remodeling rate is a risk factor for subsequent stress fracture. According to this result, preventive BP 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 either immediately prior or subsequent to the beginning of bone pain. The results from military recruits may not generalize to athletes as they represent different populations. Failure to detect increased bone remodeling either prior to or following the onset of stress fractures in athletes may stem from the measurement of serum and biochemical

markers of bone remodeling that reflect overall total body bone remodeling and are not sufficiently sensitive to detect locally accelerated bone remodeling.

Effect of bisphosphonates on fracture healing

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

In contrast to these concerns, there are now several reports suggesting that BPs 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 potential applications of BPs in orthopedics, including improved healing in distraction osteogenesis [39, 40], conserving bone architecture after osteonecrosis [35, 41, 60].

On the other hand, considering the process of bone and fracture repair consisted with an anabolic (bone forming) response and 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]. BP treatment may require an anabolic conjunctive therapy to ensure enhanced successful repair [16, 42]. This cannot be directly applied to the treatment of stress fractures as they represent different features. Assuming that most of athletes with stress fractures except some special situations (e.g. female athlete triad) have normal anabolic response in bone homeostasis, BPs as anti-catabolic agents would be considered satisfactory for the treatment of stress fractures. However, if systemic bone morphogenetic proteins as anabolic agents are available, using them in combination with BPs [42] may be more efficacious in the treatment of stress fractures.

In recent years, the dosing regimens used in treating osteoporosis have evolved such that dosing interval times are increasing. 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 once-yearly infusion [12, 21]. Previous preclinical studies using continuous BP therapy may therefore not be relevant to such

intermittent dosing regimens [5]. 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 rat femoral critical defect model [42]. Amanat et al. [5] recently reported that delaying (1 or 2 week after fracture) the single dose systemic zoledronic acid administration increased callus volume, callus BMC, and mechanical strength in a rat fracture model.

BPs 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]. The increased bone remodeling and low bone mineral density (BMD) indicate a potential role for BP therapy in LTO. Miltner et al. [51] reported a case of transient osteoporosis of the navicular bone in a 400 m splinter 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 has been shown as an effective method to treat intractable stress fracture in athletes [72]. Shock wave induces

angiogenesis-related growth factors and stimulates neovascularization, which improves blood supply and increase cell proliferation to the fracture site. Hausman et al. [29] showed that angiogenesis is essential to very early stages of fracture healing, and suggested impairment of fracture healing may be an adverse effect of clinical treatments with antiangiogenic drugs. Considering the antiangiogenesis properties [26, 65, 83], administration of nitrogen-containing BPs at initial stage of fracture healing may have an adverse effect on stress fracture treatment.

Bisphosphonates and fatigue loading

In the 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 and 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 14 days for a treatment period was too short to have any significant effect of alendronate on skeletal modeling 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 a glucocorticoid and alendronate experimentally, the expected apoptotic effect of BPs on osteoclasts was reduced [80].

Oversuppression and microdamage accumulation

Concerns have been raised about potential oversuppression of bone remodeling during long-term use of BPs. Although the administration of BPs for athletes would be relatively short-term, physicians should at least know about that. After bone uptake, the BPs are liberated again only when the bone in which they are deposited is resorbed. Thus, the half-life of BPs in bone is very long, ranging among different species from 1 to 10 years, depending largely on the rate of bone remodeling [38]. There appears to be no progression of the antiresorptive effect with time even when the compounds are given continuously, which suggests the BP buried in the bone is inactive, at least as long as it remains buried there [63]. In experiments of the ribs of dogs treated with risedronate or alendronate for 1 year, alendronate has been shown to inhibit normal repair of microdamage arising from marked suppression of bone remodeling, which in turn, results in accumulation of microdamage [2, 37, 46, 47]. When bone remodeling decreased 53% and 68%, respectively, as a result of these treatments, the corresponding increases in microcrack damage were 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 equivalent doses used to treat human osteoporosis patients, it strongly suggests that bone remodeling is necessary to prevent fatigue microdamage from accumulating in, and weakening bone.

The long-term use (5-10 years) of BPs in the therapy of osteoporosis generally 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), resulting in increased susceptibility to nonspinal fractures that heel poorly. In addition, Ott [55] speculated that long-term alendronate treatment in humans might impair mechanical strength of bone. 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 osteopetrosis-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 are associated with alendronate use. They suggested that this may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use. It has also shown that long-term suppression of bone

remodeling by bisphosphonate increases non-enzymatic cross-linking and can result in brittle bone [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 fracture, off-label use of a drug demands special caution. In the 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 to 48 hours. Since nausea was the main problem with the 90-mg dose when compared with the 60-mg dose, authors recommended using a 60-mg treatment doses. On the other hand, in randomized controlled study of military recruits, risedronate using for the prevention of stress fractures had no more side effects than placebo treatment [50].

Oral BPs can give stomach upset, inflammation, and erosions of the esophagus, which is the main problem of oral nitrogen-containing preparations. This can be prevented by remaining seated upright for 30 to 60 minutes after taking the medication. A number of cases of severe bone, joint, or musculoskeletal pain associated with oral BPs, alendronate and risedronate, have been reported [84]. These symptoms could improve after discontinuation of the drug treatment. Intravenous nitrogen-containing BPs 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], which is 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 BPs, in particular zoledronic acid, has nephrotoxic potentials [14, 30].

Now another potential complication of these agents has surfaced. There have been recent reports of osteonecrosis of the jaw (ONJ) occurring in multiple myeloma or metastatic cancer patients treated with intravenous BPs [10, 45, 67], and these reports have led to growing concern about the safety of oral BPs in patients with osteoporosis. In the literature review, Pazianas et al. [58] have identified 26 cases of ONJ in patients receiving oral BPs. Considering that millions of patients have been prescribed BPs for the treatment of osteoporosis, this prevalence of ONJ was relatively low. The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure [82]. Age ≥60 years (only 1 patient was aged <40 years), female sex, and previous invasive dental treatment were the most common characteristics of those who developed ONJ [58]. At present, there are insufficient data available to construct evidence-based guidelines for the prevention and therapy of ONJ. In the case of administration of BPs to athletes, the physician should at least check their

previous dental history and current dental condition, and inform about the low risk of developing ONJ irrespective of the route and frequency of BP administration.

Because of increased sports participation in the child and adolescent age groups, athletes with open physis are predisposed to stress fractures. There are some concerns about the impact of BPs on the open physis, chondro-osseous modeling, and consequent growth in otherwise normal long bones. Smith et al. [70] has presented from a growing animal model that nitrogen-containing BPs can cause transient effects on physeal cell morphology and retention of cartilaginous matrix coinciding with a growth disturbance (3% decrement in final long bone length) even in 6 weeks (short-term) period. On the other hand, in radiographic quantification study, Ward et al. [79] showed that clinically relevant doses of BPs did not necessarily disturb physeal modeling in the distal femur throughout childhood. In a case series of van Persijn van Meerten [77], BP treatment in children with open physis characteristically resulted in epi- and metaphyseal sclerosis, but this was a reversible phenomenon. However, we must say that there is so far a lack of evidence about the safety use of BPs for the adolescent athletes with open physis.

Although the pharmacologic activities of BPs are retained for a period of time after cessation of treatment, the effects of BPs are likely transient, and may disappear once the drug is withdrawn. Therefore, short-term exposure to BPs for the treatment of stress

fractures would not be expected to cause long-term deleterious effects on the skeleton [19].

Regarding the safety of BPs in women who are pregnant or of childbearing age, however, it has also not been clearly established. In rat studies, alendronate has been found to cross the placenta and accumulate in fetal bone [57]. The presence of alendronate may interfere with fetal bone mineralization and development. The half-life of the BPs 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 of teratogenic effects in human, to date.

Clinical intervention using BPs for stress fractures

To date, there has been no randomized controlled study about BP treatment after stress fractures. However, a case series [71] has 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 fracture, with four of five athletes having symptoms more than 5 months before treatment. A 30 mg test dose was given intravenously over 2 hours, followed by four additional

treatments at weekly intervals in 60 mg or 90 mg amounts. With the initial treatment, four of five subjects were able to continue training without symptoms within 72 hours. 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 BPs 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 about the prevention of stress fractures using oral BP. Milgrom et al. [50] conducted a study of 324 male Israeli military recruits using 30 mg risedronate or placebo daily for 10 days during the first 2 weeks of basic training period before they began any physically demanding training. After the initial 10-day loading dose, subjects received a 30-mg maintenance dose 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. Although the large 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 the subjects that received risedronate therapy before the period of strenuous activity, although this finding was not statistically significant. This observation fits with a rat model data from Barrett et al. [6]. They have suggested that short-term preemptive treatment with alendronate does 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 BPs for the treatment of stress fractures even 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 BPs on stress fracture healing in human.

Whenever we consider the treatment plan for a stress fracture, we must understand why the injury has occurred in the first place. A dynamic balance exists between

accumulation of microdamage and host repair processes. Any intrinsic and extrinsic factor that disrupts 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.). The understanding of these causes is essential before any treatment of stress fractures is started.

It is estimated that >50% of a dose of intravenous BP is bioavailable for incorporation into the bone matrix, compared with <1% of oral BP [9, 22]. Intravenous BPs have improved bioavailability and do not produce gastrointestinal side effects as oral BPs do. However, there are some possibilities of nontrivial side effects. Intravenous administration of clodronate and pamidronate require slow, prolonged infusion to avoid renal toxicity [13] and therefore must be undertaken in the hospital setting. This is inconvenient, labor-intensive, and costly and can be associated with complication [56]. Because it is self administered, on the other hand, oral BPs provide some practical advantages to administration. In either case, less-frequently administered dosage regimens may enhance compliance with BP treatment. Because of the relatively short-term administration of BPs and enthusiasm for the treatment of stress fractures,

rout of administration may give athletes no problems.

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

In a rat fracture [5] or bone defect model [42], single systemic dose and delayed administration of intravenous BP (1 or 2 week after making fracture or defect) is 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 been increased because of increased availability of target mineral binding sites. Alternatively, the delay may have allowed the anabolic response to gather pace before administration of BPs. On the other hand, an animal study [6] and clinical study [50] suggested brief preemptive 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 their repair process at the time of treatment, it is not necessary to delay the administration of BPs for the treatment of stress fractures in athletes.

Oral BP 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 BP treatment will cause more severe side effects than that of oral BP treatment. If high-dose of oral BPs is used to compensate their low bioavailability, it may rather cause more problems in view of the safety. For adolescent with open physis and women who are of childbearing age, the safety use of BPs has not yet established. Therefore, current studies of the use of BPs 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 then be initiated [32].

The question remains what kind of BPs we should use for the treatment of stress fractures. This seems likely because there is no theoretical basis for other BPs to behave differently. Furthermore, when not given in excess, many BPs have a positive effect on mechanical properties of bone. However, further researches are required to compare the

different type of BPs about 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 BPs 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. Until the results of the well-designed clinical trials are available, it is prudent to limit the use of BPs in the treatment of stress fractures.

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