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# How do bisphosphonates affect fracture healing?

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ABSTRACT

Bisphosphonates (BPs) have been in use for many years for the treatment of osteoporosis, multiple myeloma, Paget's disease, as well as a variety of other diseases in which there is reduced bone mineral density. Given that bisphosphonates inhibit bone resorption, an important stage of fracture healing; this class of compounds has been widely studied in preclinical models regarding their influence on fracture healing. In animal models, bisphosphonate treatment is associated with a larger fracture callus, coincident with a delay in remodeling from primary woven bone to lamellar bone, but there is no delay in formation of the fracture callus. In humans, *de novo* use of bisphosphonate therapy after fracture does not appear to have a significant effect on fracture healing. Rarely, patients with long term use of Bisphosphonates may develop an atypical fracture and delay in fracture healing has been observed. In summary, bisphosphonates appear safe for use in the setting of acute fracture management in the upper and lower extremity in humans. While much remains unknown about the effects on healing of long-term bisphosphonates, use prior to "typical" fracture, in the special case of atypical fracture, evidence suggests that bisphosphonates negatively influence healing.



## Introduction

Bisphosphonates have been in clinical use since 1968 (etidronate), and use of these compounds has increased in prevalence after the Food and Drug Administration approved alendronate for use in September of 1995. As such, millions of doses of bisphosphonates (BPs) have been taken worldwide and we have now begun to collect and analyze critical data regarding acute, as well as long-term consequences of their use. Herein, we will examine the current best evidence regarding the effects of bisphosphonate use on fracture healing, including evidence from animal models, as well as human studies, with the aim to inform the reader about the implications of bisphosphonate use on bone healing.

Fracture repair is a complex, multi-staged process, of which the end goal is the return of the damaged bone to a functional and biomechanically sound state. Immediately post fracture, bleeding occurs and this is followed by the formation of a hematoma at the fracture site. This creates an inflammatory environment that recruits mesenchymal stem cells (MSCs) to the site of healing, followed by expansion of these cells and their differentiation into either osteoblasts or chondrocytes. Via intramembranous ossification, the osteoblast cells form new bone on the existing bone surface, flanking the fracture site, generating the hard callus. In the center, over the site of fracture, which is a more hypoxic environment and one that is less mechanically sound, chondrocytes form a cartilaginous or soft callus via endochondral ossification. As the chondrocyte population expands, these cells become hypertrophic and the cartilage tissue is mineralized. The callus is then invaded by the vasculature, allowing for infiltration by osteoclasts that in turn remove the mineralized cartilage allowing for the ultimate bridging of the fracture by woven bone. This is followed by a secondary and more prolonged remodeling phase, which includes resorption by the osteoclasts, which converts the woven bone to lamellar bone, and remodeling of the original fractured bone below the callus, yielding bone that mechanically and anatomically matches the pre-fractured bone [1,2].

All bisphosphonates (BPs) are analogues of inorganic pyrophosphate, wherein a carbon, in place of the natural oxygen, connects the two phosphates. As a result, BPs have two side chains that can be modified to modulate their pharmacological properties. Clinically used BPs can be divided into non-nitrogen containing compounds such as etidronate, clodronate, tiludronate and nitrogen containing BPs such as pamidronate, alendronate, ibandronate, risedronate and zoledronate. All BPs have a high affinity for calcium and in the body, they concentrate in the skeleton at sites of active bone remodeling. Both classes of BPs become embedded in new bone during the anabolic phase of remodeling by binding to the hydroxyapatite of bone, where they remain inert. When bone containing a BP is resorbed the BPs are released in the acidic lacuna created by the osteoclast, and are taken up by these cells. The non-nitrogen containing BPs induce apoptosis in the osteoclast by incorporating into

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ATP and thereby reduce resorption by decreasing the number of active osteoclast cells on the bone surface. The more widely used nitrogen containing BPs inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway. This results in cytoskeletal changes in the osteoclast, which inhibit the activity of the osteoclast and or may induce apoptosis of these cells. Similar to the non-nitrogen containing BPs, the net result is a decrease in osteoclastic bone resorption. Because these compounds become entombed in the bone, they reside in the body long after treatment cessation and indeed, the calculated half-life of elimination of BPs from the skeleton is up to 10 years [3]. This is substantiated by the observation of detectable levels of pamidronate in the urine of patients 8 years after they had ceased treatment [4]. Given that resorption of bone by the osteoclast is a key component of fracture repair, concerns have been raised regarding BP associated inhibition of the repair process, both in situations where there has been past use of these compounds and it is known that BPs have been retained in the skeleton and in cases of acute treatment after fracture.

## Materials and methods

A literature search of Medline, Google Scholar and PubMed was performed for articles addressing the subject of bisphosphonates on fracture healing and this literature search yielded 275 citations (search conducted in December, of 2014). Included among our search findings were two recent reviews of meta-analyses of human studies and these papers were not considered as a primary reference, yielding 273 papers for consideration [5,6]. Several of the articles identified addressed the topic of preclinical fracture healing with bisphosphonates. In addition to database queries, the reference lists of potentially relevant articles were also examined to identify additional relevant studies. Inclusion criteria for consideration of studies for this literature review included: 1) papers were written in English, 2) publication of the study findings in peer-reviewed journals and 3) in vitro and in vivo studies that evaluated the implication of Bisphosphonates on fracture healing. We used the following exclusion criteria: 1) articles using languages other than English and 2) letters, reviews, expert opinion publications or other articles that were not primary reports of findings. Articles meeting the above mentioned criteria were retrieved and all of the studies related to these were extensively reviewed.

## Results

The search strategies yielded a total of 273 potential articles. During the selection process, the articles were excluded by title and or by abstract, because they were clearly irrelevant to the study question. The papers meeting our inclusion criteria are described in greater detail below. These papers could be distributed into two main categories. The first category was comprised of studies which investigated the effects of BPs in animal models and the second category included the studies which examined effects of BPs use on human fracture healing.

### *Preclinical animal models*

Several animal models have been used to examine the effects of BPs on fracture healing including mice, rats, rabbits, dogs and ovine models. Using these models, the impact of bisphosphonate administration on indirect fracture healing (healing with callus) has been extensively examined and the results have been remarkably consistent, but direct fracture healing has been less well studied. Overall, these studies of indirect healing suggest that BP administration appears to decrease the remodeling of fracture callus with a concomitant increase in fracture bridging and or retained cancellous bone structures within the callus [7,8] but it is apparent that BPs do not interfere with the formation of the callus itself [8–15]. As a result, there is a delay in the conversion of the woven bone at the fracture to mature lamellar bone [16].

### *Indirect fracture healing*

Fu and colleagues studied fracture callus properties in ovariectomized rats using alendronate long-term and found a larger fracture callus formed in the treated animals. However, despite the observation of a delayed conversion of woven bone to lamellar bone in the intervention group, the mechanical properties of the callus were similar to control animals [16]. Manabe et al. found similar findings using ibandronate. In this study, the authors noted that extending the dosing interval could mitigate the delay of conversion of woven bone to lamellar bone in the callus [17].

Kidd and colleagues studied the effects of either a high or low dose of risedronate on stress fracture healing in a rat ulna model. In the animals treated with the higher dose (1.0 mg/kg, twice the normal dose for osteoporosis treatment), they found a delay in healing. Specifically they noted a reduction in bone resorption and in new bone formation along the fracture line at 6 and 10 weeks post fracture. This delay in healing was not observed in the animals treated with a low dose (0.1 mg/kg). Regardless of the dose of risedronate used, they observed no interference with callus formation [18]. Sloan and colleagues had similar findings study in which the effects of alendronate were examined [19].

Yu and colleagues noted that early in fracture repair, there was a delay in cartilage hypertrophy and in angiogenesis and later in the repair, there a delay in remodeling of the callus, cartilage and bone in mice treated with zoledronate. This effect was more pronounced in mandible fracture healing than tibia fracture healing in their study [20]. It must be note though that this is in stark contrast to studies in rabbits, in which use of zoledronic acid was observed to accelerate mandible fracture healing [21].

Bosemark et al. used a combination of zoledronate and BMP7 in an autograft healing model in rats. While they did observe an effect of just BMP7 alone, the combined therapy resulted in a substantial increase in callus volume and a four-fold increase in mechanical strength at the healed fracture site as compared to the repair observed in the controls. The impact of the combined therapy was nearly double that for the BMP7 treatment alone with regards to callus volume and ultimate force at failure at the fracture site [22]. In a follow up study, this same group examined the combination of BMP7 and zoledronate on healing in an allograph model and found a very similar result [23]. Doi and colleagues examined the impact of zoledronic acid plus BMP2 in a rat femoral fracture model and determined that healed fractures from rats treated with either zoledronic acid alone or zoledronic acid combination with BMP2 showed greater ultimate load at failure and greater stiffness than either the control treated animals or the animals treated with BMP2 alone. The authors further concluded that the combination of BMP2 and zoledronic acid enhanced fracture fusion [24].

Another group studied low-intensity, pulsed ultrasound combined with alendronate in a rat osteotomy model, wherein the fracture was fixed with intramedullary pin. An increase in bone mineral density at the osteotomy site was observed in the ultrasound treatment alone group, the alendronate treatment alone group and in the combined treatment groups, with the greatest effect seen in the combined treatment animals. However, no mechanical testing of the healed bone was conducted in this study [25].