Skeletal Accumulation of Bisphosphonates: Implications for Osteoporosis Treatment

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Abstract

Background: Bisphosphonates (BPs), the gold-standard pharmacological treatment for osteoporosis, are unique in that they become physically bound to the bone matrix and therefore accumulate over time. This skeletal accumulation has important physiological implications which are not completely understood. Objective: To review concepts related to the biological effects of BP accumulation within the skeleton. Methods: Articles concerning the topic of skeletal accumulation of BP treatment were identified. Results/Conclusions: Skeletal accumulation of BP, dictated by both chemical and biological factors, is dose-dependent, differs among skeletal sites, and likely differs among the various BPs. BP embedded within the skeletal matrix has lasting biological effects, the results of which have both positive and negative implications for bone remodeling. As alternative anti-remodeling agents gain approval for treatment of osteoporosis, the property of skeletal accumulation will likely be unique to bisphosphonates and therefore may be the property that determines the future use of this drug class.

Key words: anti-remodeling agents, bisphosphonates, osteoporosis treatment, osteonecrosis of the jaw, remodeling suppression
1. Introduction

Bisphosphonates (BPs) have become the gold-standard pharmacological treatment for osteoporosis, numerous other metabolic bone diseases, and for reducing skeletal complications associated with cancers [1, 2]. BPs produce their effect, whether it be reducing fracture risk in postmenopausal women or reducing hypercalceimia of malignancy in cancer patients, by suppressing bone remodeling [2]. Although other pharmaceutical agents exist for reducing bone remodeling (estrogen/hormone replacement therapy, calcitonin, selective estrogen receptor modulators), BPs produce the most robust reduction in bone remodeling.

The mechanism of action for BPs on bone has recently been expertly reviewed [1]. In summary, after uptake by osteoclasts via endocytosis, nitrogen-containing BPs (e.g. alendronate, risedronate, pamidronate, ibandronate, zoledronate) inhibit key enzymes in the mevalonate pathway, preventing the generation of lipids necessary for the prenylation of small GTPase proteins. This in turn results in a significant reduction in the ability of osteoclasts to resorb bone and therefore a reduction in bone loss. Non-nitrogen containing BPs (etidronate, clodronate) act through an alternative mechanism, in which toxic metabolites, resembling ATP, accumulate and ultimately result in reduced resorption and bone loss. These mechanisms of remodeling suppression (either inhibition of protein prenylation or accumulation of toxic metabolites) are unique to BPs, as compared to other anti-remodeling agents such as estrogen or calcitonin. BPs have an additional uniqueness among the numerous anti-osteoporosis agents in that they are retained within the body long-term. Due to their high skeletal affinity and strong binding
properties, BPs become physically bound to the bone matrix. This skeletal accumulation has important physiological implications which are not completely understood.

2. The chemistry and biology of bisphosphonate accumulation in the skeleton

2.1 Chemistry. Bisphosphonates all have a common phosphate-carbon-phosphate (P-C-P) moiety as part of their basic structure [3]. While the central portion of the BP structure is analogous to that of naturally occurring inorganic pyrophosphate, the substitution of a central carbon atom in BPs for the central oxygen atom of pyrophosphates confers a resistance to chemical and enzymatic breakdown [4]. This allows BPs to either bind to the skeleton or be excreted. Attached to the central P-C-P core are two side chains (termed R1 and R2). Each BP differs in its side-chains, which are primarily responsible for the binding affinity to mineral and biochemical activity on osteoclast enzyme activity.

The mineral binding affinity of the BPs determines the probability of attachment to mineral and the strength of the binding. Using in vitro methods, the binding affinities of several BPs to mineral has been established as clodronate < etidronate < risedronate < ibandronate < alendronate < pamidronate < zoledronate [5, 6]. This means that all things being equal, zoledronate would have the greatest attraction for and strongest attachment to mineral. In addition to the strength of mineral attachment, BPs show different accumulation capacities for binding to mineral in vitro which result from differences in electrical charges [5]. Those BPs with more positive charges (alendronate, ibandronate, zoledronate) are thought to have greater accumulation potential than those with more
negative charges (risedronate) [5]. It is hypothesized that this effect of surface charge
alterations may play a role, independent of mineral affinity, in binding capacity and
therefore skeletal accumulation [1]. This elegant work highlights the complexity of the
physical-chemical properties of BPs which serves as the foundation underlying skeletal
accumulation of BP. Yet equally important, and equally complex, for determining
skeletal accumulation are the various biological aspects of in vivo administration.

2.2 Biology. The high affinity of bisphosphonates for hydroxyapatite results in the
majority of the drug becoming bound to the skeleton upon dosing with the remaining
being cleared, unmetabolized, primary through the kidney. While in the circulation,
bisphosphonates bind the plasma proteins, predominantly serum albumin, in a
concentration-, pH-, and-calcium concentration- dependent fashion [7, 8]. Based on data
from several species (rats, dogs, monkeys) between 56-66% of BP is retained in the
skeleton 24 hr post dose, the majority of which is incorporated within the first 6 hours
[9]. For a given dose the skeletal uptake of BP is saturable yet for repeated dosing it is
non-saturable [10]. Using a wide range of doses (0.1 to 50 mg/kg), administered to rats
as a single IV injection, there was a linear relationship between dose and skeletal
concentration up to 5 mg/kg with a less than proportional increase thereafter [10].
Interestingly similar skeletal saturation does not occur when high doses (e.g. those that
show saturation with a single dose) are broken up into multiple doses [10]. Several
longer-term experiments confirm this lack of skeletal saturation with repeated dosing in
both rat and dog models [10-16]. This means consideration of cumulative dose, as
opposed to amount of drug for each dose, is the key factor when considering skeletal accumulation.

In addition to dose, the route of administration plays a significant role in determining skeletal accumulation. A major limitation of oral dosing is the low bioavailability, the amount of drug that reaches the systemic circulation. Interestingly, oral absorption which occurs primarily in the stomach and upper aspect of the small intestine [17, 18], is nonlinearly dose-dependent; increasing the oral dose from 2 to 40 mg/kg results in changes in bioavailability of the drug from 0.5% to 5% [18]. This has potentially significant implications with respect to the trend toward higher, less frequent dosing regimens. For example, oral alendronate can be taken as a daily (10 mg) or weekly (70 mg) dose; oral risedronate as a daily (5 mg), weekly (35 mg), or monthly (150 mg) dose; ibandronate can be taken as a daily (2.5 mg) or monthly (150 mg) oral dose or a quarterly (3 mg) intravenous dose. This means that skeletal accumulation in patients treated early in the life of alendronate (daily dosing) is likely lower than those treated with the more recent weekly dosing. The transition to intravenous dosing, which overcomes the low bioavailability of oral dosing, also leads to significantly higher levels of skeletal accumulation relative to oral dosing [9]. Even when attempts have been made to match bioavailability between oral and intravenous dosing (giving 10-fold higher doses orally) there was still 10-fold higher plasma concentration and a 30-fold higher concentration of skeletally-bound BP with IV dosing [19]. These disproportional changes suggest there are additional effects, beyond just higher plasma concentrations, related to intravenous dosing that dictate skeletal uptake.
Skeletal accumulation of BP is not homogenous across bone sites. Although limited data exists, sites with higher remodeling are thought to accumulate greater amounts of drug [12]. The accumulation at such sites is postulated to be due to a greater amount of actively resorbing surface which is known to preferentially bind BP [20]. Alternatively, it could be that sites with higher remodeling have greater metabolic demands and thus have higher blood flow. It has been shown that the site-specificity of BP accumulation is dose [14] and duration dependent [21]. It is also plausible that there may be differences in site-specificity among the bisphosphonates and/or by route of administration highlighting the complexity and interaction among all the biological factors.

Another important consideration with respect to accumulation of BP is the disassociation of bound drug from the skeleton. In vitro, hydroxyapatite-bound BP is liberated during resorption due to the locally acidic environment produced by the osteoclasts [20]. Data concerning dissociation come from two different dog studies. Following one year of treatment with pamidronate, animals were allowed an additional year of treatment withdrawal followed by assessment of skeletal concentrations in the ilium, stenum, and vertebra [14]. Although all bone sites had significantly less pamidronate at year 2 compared to year one, the change was greatest in the vertebra [14]. Similar results were found in the rib in studies using etidronate [22]. These data suggests the dissociation is greatest at sites with the highest metabolic activity even if that activity had been reduced by BP-treatment.
Taken together, these data begin to unravel the mechanisms, both chemical and biological, underlying skeletal accumulation of BP. The underpinning is clearly in the physical interaction between BP and hydroxyapatite brought about by the chemical structure/charge. Yet accumulation is strongly dependent on biological aspects including dosing level, route of administration, skeletal sites, duration of treatment, as well interactions among these factors. To add another level of complexity, each BP has its own chemical and biological properties making it necessary to consider each of them separately [17]. Thus while each property, specifically those related to the biological aspects of accumulation, have been worked out for some of the BPs, the results are not likely applicable to all BPs.

3. The clinical implication of bisphosphonate accumulation in the skeleton

The focus on skeletal accumulation of bisphosphonates is ultimately aimed at understanding if/how it affects skeletal health. BP within the skeleton retains the ability to exert anti-remodeling effects once it is liberated from the skeleton. This has significant implications with respect to determining whether and how to treat patients’ long term. Specifically, the question is whether it is necessary for indefinite treatment or whether drug holidays (periodic cessation of treatment) could be utilized without compromising efficacy. Additionally as data suggests reduced efficacy of anabolic agents in patients who have been treated with BPs, it is important to understand how effectively BP-induced remodeling suppression reverts to basal levels if alternative pharmaceutical treatments are warranted. Although these two concepts represent the majority of clinical interest in bisphosphonate accumulation, the concept of skeletal
accumulation has been brought to the forefront of bisphosphonate research recently with the emergence of a condition known as osteonecrosis of the jaw (ONJ). Despite the lack of a definitive cause/effect relationship between BPs and ONJ, much speculation exists concerning such a relationship and this speculation involves skeletal accumulation of BP as a contributing factor.

### 3.1 Continued remodeling suppression and fracture risk reduction following bisphosphonate treatment withdrawal

The most definitive clinical data concerning the skeletal effects following withdrawal of BP-treatment come from a recent study of Black et al [23]. Building on the initial Fracture Intervention Trial (FIT) study which treated patients for 5 years with placebo or alendronate [24, 25], the Fracture Intervention Trial Long-term Extension (FLEX) was designed to follow a subset of alendronate-treated patients for an additional 5 years with either continued alendronate treatment or placebo [23]. The results of this study show that women who were switched to placebo treatment lost a significant amount of bone density over the 5 year period although their BMD remained well-above baseline values. Biomarkers of bone remodeling of patients who stopped alendronate treatment were higher than those of patients who continued treatment, yet also remained significantly lower compared to baseline. While this study was not powered to detect differences in fractures between the two groups, there was not even a trend toward differences in clinical fractures between women who stopped treatment compared to those who continued. Subsequent subgroup analyses, again limited by statistical power, suggest women at the highest risk of fracture benefit most from continued treatment while those
with adequate response to 5 years of treatment could be considered for a drug holiday.

The ideal duration for such a drug holiday, or criteria by which to base resuming treatment, were not addressed by the authors. Despite the limitation concerning power to detect fractures, this study is significant as it is likely to be the best data to be generated concerning treatment withdrawal [26] unless similar extensions of large-scale follow-ups to other clinical trials are undertaken. Other retrospective data concerning withdrawal from BP-treatment do suggest there may be a minimal treatment duration prior to withdrawal that is necessary in order to have sustained fracture risk efficacy [27]. Those patients treated for 2 years at the time of treatment withdrawal had significantly higher number of fractures compared to those who continued treatment; this was not the case in patients treated >2 years prior to withdrawal [27, 28]. Taken together, these limited data provide support for drug holidays in some BP-treated patients, most notably those who have been treated for several years with robust BMD responses to these years of treatment.

Additional smaller sets of clinical data do exist regarding bone turnover biomarkers and/or BMD after treatment withdrawal. These studies show that upon treatment withdrawal, the rate of bone density decline is similar in patients previously treated with alendronate as those treated with placebo although the alendronate-treated patients remain with higher BMDs [29, 30]. Additionally, numerous studies show that although bone turnover biomarkers revert back toward placebo-treated patient levels after withdrawal they remain significantly lower up to seven years post-withdrawal [29-33]. An important factor, given the clear difference in skeletal accumulation among the
different bisphosphonates, is that the majority of clinical data concerning treatment withdrawal are in patients treated with daily oral alendronate. As other bisphosphonates and other treatment regimens gain sufficient patient populations, clinical data may become available in the future.

Preclinical studies provide data on the effects of BP withdrawal that complement these clinical studies. Using ovariectomized rats, the benefits of risedronate on trabecular bone mass preservation and suppression of bone remodeling that occurred following 6 months of treatment were maintained through 6 months of withdrawal but, in general, were completely lost after 12 months [34]. These findings are supported by studies with incadronate, which additionally showed that changes during withdrawal were dose dependent as higher doses maintained benefits four times longer upon withdrawal [35]. In the lone pre-clinical comparison between two BPs, ovariectomized rats were treated with either alendronate or risedronate (at doses consistent with those used clinically on a mg/kg basis) for 8 weeks and then withdrawn for up to 16 weeks [36]. This study showed trabecular bone formation rate returned to levels comparable to controls in risedronate, but not alendronate treated animals [36]. These data highlight the BP-specific responses to treatment withdrawal, which the authors postulated could be the result of different binding affinities between the two drugs. Overall, these pre-clinical data support the clinical studies in showing that 1) there is a clear effect of treatment dose and/or duration on the withdrawal response and 2) each bisphosphonate is likely different in these responses.
3.2 Influence of continued remodeling suppression during treatment withdrawal on subsequent anabolic efficacy

The residual effects of continued remodeling suppression following BP-treatment do not come without a cost, one of which is a potential compromised response to subsequent treatment with anabolic agents. Anabolic treatment for osteoporosis, of which parathyroid hormone (PTH) is currently the only FDA approved agent, stimulate bone modeling/remodeling to increase bone mass and is indicated for patients with severe osteoporosis. The most likely scenario in which anabolic treatment would follow bisphosphonate treatment is if a patient fails to adequately respond to BP-treatment and necessitates other means of enhancing bone mass. The clinical data show that when PTH is given either concurrently with [37, 38] or after cessation of [39, 40] alendronate, there is a significant blunting of the anabolic effect as determined by changes in BMD and remodeling biomarkers. Interesting, the same is not true following treatment with risedronate which, when withdrawn, allows significant PTH-induced increases in bone turnover markers and BMD [40]. These bisphosphonate-specific interactions with anabolic treatment are supported by pre-clinical studies [41].

3.3 Proposed connection between skeletal accumulation and osteonecrosis of the jaw

The condition of osteonecrosis of the jaw (ONJ) continues to be an enigma surrounding BP-treatment, albeit predominately within the context of high doses to cancer patients [42, 43]. Despite the lack of definitive proof directly linking BPs and ONJ, enough indirect evidence exists to justify discussion of potential mechanisms underlying this condition. It has been hypothesized that the focal loss of osteocytes [44] [45] and their
canalicular network [45] with BP-treatment are a part of ONJ pathophysiology [46].

Loss of osteocyte viability could simply be an unintended consequence of reduced remodeling, which would allow regions containing osteocytes that die of normal causes to accumulate over time. The remodeling rate of the mandible is one of the highest among skeletal sites [47, 48] and therefore the significant reduction in remodeling that occurs in the mandible with BP-treatment [45] would lead to the natural accumulation of non-viable regions. If this is the mechanism through which regions of necrosis develop, then the issues described above with respect to recovery of bone remodeling following treatment withdrawal become imperative with respect to ONJ treatment and prevention.

An alternative explanation for accumulation of non-viable osteocytes is through a more direct pathway in which BPs have direct cytotoxic effects on osteocytes [46, 49]. In vitro studies have shown that when cultured in high concentrations of bisphosphonate, nearly every cell type has the capacity to internalize the drug, which in turn results in cell death. The effects of BPs on osteogenic cells (osteoblasts/osteocytes) in culture show a clear dose-dependent response with low concentrations suppressing apoptosis [50] and higher concentrations enhancing apoptosis [51]. The fundamental question underlying the idea of BPs having cytotoxic effects of osteocytes therefore lies in whether or not these matrix-entombed cells are exposed to sufficient concentrations of the drug. Conventional wisdom is that in vivo, BPs are localized predominately to bone surfaces adjacent to marrow (endocortical and trabecular surfaces), with preferential binding to sites actively undergoing resorption and formation [20, 52]. Recently, however, it has been shown that systemically administered bisphosphonate reaches, and becomes embedded in, the
walls of osteocyte lacunae [53]. Despite this proof-of-concept showing that BPs have access to the osteocyte-canalicular network in vivo, it remains unknown whether or not sufficient quantities accumulate that could have cytotoxic effects on the resident osteocytes.

4. Future Directions

Future interest concerning skeletal accumulation of bisphosphonates is dependent on the overall interest in bisphosphonates as an osteoporosis treatment. In turn, interest in bisphosphonates as a treatment may depend on the biological effects of skeletal accumulation. Several newer generation anti-osteoporotic treatments are on the horizon and although not yet approved by the FDA, these agents are likely to reduce fracture risk through mechanisms which differ from bisphosphonates. It is unlikely, however, that future agents will accumulate in the skeleton leaving this a property that will remain unique to bisphosphonates.

Skeletal accumulation may ultimately dictate the role bisphosphonates play in skeletal biology, both related to osteoporosis treatment as well as in other metabolic bone condition. As such much work needs to be done to understand 1) key properties of skeletal accumulation for newer generation bisphosphonates, 2) the residual biological effect of all bisphosphonates following treatment withdrawal as it relates to drug holidays and 3) any potential adverse effects associated with skeletal accumulation. The newest generation of bisphosphonates, ibandronate (either monthly oral or quarterly intravenous dosing) and zoledronate (yearly intravenous dosing), lack data concerning skeletal
accumulation. As these specific bisphosphonates utilize higher, less frequent dosing as well as different routes of administration compared to the more traditional bisphosphonates (risedronate and alendronate), it is essential to understand how these specific agents, dosing levels, and dosing routes influence skeletal accumulation. The need for greater understanding of residual effects of bisphosphonates following treatment withdrawal is true for all bisphosphonates. Specifically, it will be important to understand how treatment duration influences the withdrawal response and whether or not there are different optimal durations of treatment if the goal is to sustain an effect following treatment withdrawal as opposed to if the goal is to reverse an effect upon withdrawal. Finally, it is essential to determine if there are any adverse effects associated with skeletal accumulation and therefore any benefits to utilizing drug holidays. The emergence of jaw necrosis associated with bisphosphonate treatment, most notably in patients treated with high intravenous doses for cancer therapy, has sparked concern about potential adverse effects of accumulation although this hypothesis remains untested. Whether or not there is merit to this hypothesis, the general understanding of the long-term biological consequences of skeletal accumulation on bone cells is certainly warranted.

Many of these questions are limited by the difficulty in measuring BP concentrations in biological tissues. Much of the pre-clinical data on alendronate utilized radioactive-labeled drug [9, 10, 52] which presents unique challenges for many laboratories and also could limit its transition to large animal models and to humans. It is possible to measure BP concentrations in biological fluids and then estimate concentrations in the skeleton.
although this does not allow differences among skeletal sites to be investigated [54]. Skeletal extraction and quantification of BP, although possible, is not widely utilized due to the need for specialized equipment and technical expertise [13, 55]. An emerging area of advancement is imaging of bisphosphonates that have been fluorescently-tagged. These techniques include bulk assessment of skeletal accumulation [56, 57], histological imaging of fluorescent signal [57-60] and, most excitingly, non-invasive in vivo imaging [57, 61]. Future work in this field could significantly boost the understanding of BP accumulation in the skeleton.

5. Conclusions

Skeletal accumulation of bisphosphonates, driven by both chemical and biological factors, is dose-dependent, skeletal site-specific, and differs among the various bisphosphonates. Once embedded within the matrix, bisphosphonates can be liberated by osteoclast-mediated bone resorption, effectively recycling the drug in an active form. This drug recycling leads to continued remodeling suppression, and an apparent continued reduction in fracture risk following treatment withdrawal. Although these sustained effects seems to require some minimal duration of treatment prior to withdrawal, there is increasing evidence to support the concept of bisphosphonate ‘drug holidays’, especially in those patients who robustly respond (based on BMD) to the initial years of treatment. Continued remodeling suppression following treatment withdrawal, which differs among the various bisphosphonates, blunts the effect of anabolic treatments which could be a significant drawback in patients that necessitate alternative means of increasing bone mass. The recent implication of skeletal accumulation in the
pathophysiology of jaw osteonecrosis has also raised concern about long-term
consequences of skeletal accumulation although data are completely lacking on this
subject. As new generation anti-remodeling agents begin to emerge, the property of
skeletal accumulation will likely be unique to bisphosphonates and therefore could be the
property that determines the future use of this drug class.

6. Expert Opinion
Bisphosphonates have revolutionized the prevention and treatment of osteoporosis while
simultaneously helping advance the basic understanding of skeletal biology. While quite
a bit is known about bisphosphonates, there is much that remains unknown including
nearly all aspects related to skeletal accumulation. The idea of skeletal accumulation has
been acknowledged since the inception of BPs with some of the most in-depth studies
concerning this issue conducted in the early years of BP development. These pre-clinical
studies highlighted that skeletal accumulation is a multi-factorial process, dictated by
dose, route of administration and duration of treatment. Subsequently, as newer
generation bisphosphonates have entered the market, it has become clear that differences
exist in the kinetics and biological consequences of bisphosphonate skeletal
accumulation. In fact, skeletal accumulation differences and their associated biological
effects may be the most prominent distinguishing feature among the various
bisphosphonates. With additional understanding of skeletal accumulation differences
among the various bisphosphonates, it could be possible use specific bisphosphonate for
patients depending on their situation. For example, if the goal is only transient
suppression of remodeling or if there is a potential for anabolic treatment in the future, a
bisphosphonate which has accumulation properties that favor more rapid reversal may be preferred. Conversely, for a patient who is perceived to necessitate long-term remodeling suppression might be better served using a bisphosphonate which has sustained effects after withdrawal. The latter scenario could also incorporate intermittent drug holidays into the treatment regimen.

Neither the risk nor the benefits of drug holidays are truly understood. Although clinical data concerning bisphosphonate drug holidays are limited, they are encouraging in that fracture risk reductions can be maintained in certain patients. Thus, it seems warranted for physicians to consider their use especially for patients who have been treated with alendronate and have shown a robust BMD response. The data for risedronate suggest a more rapid loss of BP effect upon withdrawal, while no data exist for the other bisphosphonates, making the use of drug holidays in patients treated with these BPs less clear. If drug holidays are undertaken, vigilance is necessary on the part of the health care provider to track BMD and/or biomarker data and resume treatment when such markers dictate. Unfortunately, there are no established criteria for at what point to resume treatment. Given the difficulty associated with defining such criteria, they may never exist.

So the question ultimately becomes whether there is any benefit to a drug holidays. The safety profile of bisphosphonates has been exemplary and as such there has been little need to seriously explore drug holidays. The emergence of jaw necrosis, as well as recent reports of atypical femoral fractures, has sparked concern with respect to safety,
specifically over the long term. The exact role of BP-treatment in general, and more specifically skeletal accumulation, is unclear in both of these situations. Even if they do play a role, however, it isn’t clear that temporarily cessation of treatment would have any effect. Until these two aspects are clarified, the benefit of bisphosphonate drug holidays should be considered minimal. This means that at this point, while there is little risk to utilizing drug holidays is select patients, there is also little clear benefit.

Bisphosphonates will likely remain a mainstay for treating metabolic bone diseases in the near future. Given the unique property of skeletal accumulation among anti-remodeling agents, they could potentially retain a significant role for much longer. However, in order to do so, additional work must be undertaken to understand the intricacies of skeletal accumulation and how to best utilize it to serve the needs of patients.

**Reference**

   *An elegant review encompassing numerous aspects of bisphosphonates by authors who have made major contributions to the field. A must read for those interested in bisphosphonates.*


   *Although more recent articles exist, this paper represents the views of two of the most prominent names in the development of bisphosphonates.*


This paper, combined with reference 9, are the most in-depth references concerning measures of bisphosphonate uptake into the skeleton.


An in-depth pre-clinical assessment concerning the effects of treatment withdrawal on various aspects of bone (BMD, remodeling, mechanics). Additionally, it clearly shows the differences between alendronate and risedronate in post-treatment recovery of bone remodeling.


Dental & Orthopaedic Implants, 3rd Annual Indiana Conference. Indianapolis, IN 1998.


