INSTRUCTIONAL REVIEW

Long-term bisphosphonate usage and subtrochanteric insufficiency fractures
A CAUSE FOR CONCERN?

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For over a decade, bisphosphonate administration has evolved and become the cornerstone of the prevention and treatment of fragility fractures. Millions of post-menopausal women have relied on, and continue to depend on, the long-acting, bone density-maintaining pharmaceutical drug to prevent low-energy fractures. In return, we have seen the number of fragility fractures decrease, along with associated costs and emotional benefits. However, with any drug, there are often concerns with side effects and complications, and this unique drug class is seeing one such complication in atypical subtrochanteric femoral fracture, counterproductive to that which it was designed to prevent. This has created concern over long-term bisphosphonate administration and its potential link to these atypical fractures. There is controversial evidence surrounding such a definitive link, and no protocol for managing these fractures.

This review offers the latest information regarding this rare but increasingly controversial adverse effect and its potential connection to one of the most successful forms of treatment that is available for the management of fragility fractures.

Approval of the first bisphosphonate, alendronate, provided hope for post-menopausal women across the globe with regards to the prevention of low-energy fractures. Clinical trials were very promising as they reported a significant decrease in the incidence of fractures of the spine and hip, with a concomitant reduction in associated costs and health care utilisation. Today, this class of drug has expanded to include several readily available compounds and is widely considered first-line therapy and the mainstay of primary and secondary fragility fracture prevention (Table I).

However, despite short- and mid-term success, over the past five years, there has been growing concern over long-term bisphosphonate use and its associated increased risk of atypical subtrochanteric fracture of the femur. This has become a very controversial topic that now occupies the minds and readerships of journals, medical and surgical alike, with a recent further increase of reports in the literature, which have left care providers wishing for evidence-based recommendations regarding this rather confounding practice management conundrum. The purpose of this review is to provide a synopsis of the bisphosphonate group of drugs, including the mechanism of action at the molecular level, a review of the clinical trials proving their efficacy and most importantly, an in-depth and up-to-date summary of the literature, potential rationale and any current recommendations concerning these atypical fracture presentations.

Evolving understanding of the mechanism of action of bisphosphonates

In the late 1960s to 1970s, much intrigue surrounded the potential role of bisphosphonates. This unique class of drug acted as non-hydrolysable, or chain-terminating, analogue of pyrophosphate, which is a ubiquitous molecule used by several biochemical reactions throughout the body. Despite mimicking a widely distributed chemical backbone, essential for a large number of cellular processes throughout the body, this analogue class was different in that it exhibited a specific affinity for bone cells. This has become a very controversial topic that now occupies the minds and readerships of journals, medical and surgical alike, with a recent further increase of reports in the literature, which have left care providers wishing for evidence-based recommendations regarding this rather confounding practice management conundrum. The purpose of this review is to provide a synopsis of the bisphosphonate group of drugs, including the mechanism of action at the molecular level, a review of the clinical trials proving their efficacy and most importantly, an in-depth and up-to-date summary of the literature, potential rationale and any current recommendations concerning these atypical fracture presentations.

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Table I. Generic and brand names of commonly used N-BPs (alendronate, ibandronate, pamidronate, risedronate, and zoledronate), and the n-BP subclasses (etidronate, tiludronate)

<table>
<thead>
<tr>
<th>Subclass and generic name</th>
<th>Brand name (manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen-containing bisphosphonates (N-BPs)</td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>Fosamax (Merck, Whitehouse Station, New Jersey)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Boniva (Roche, San Francisco, California)</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Aredia (Novartis, East Hanover, New Jersey)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Actonel (Warner Chilcott, Rockaway, New Jersey)</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Reclast (Novartis, East Hanover, New Jersey)</td>
</tr>
<tr>
<td>Non-nitrogen-containing bisphosphonates (n-BPs)</td>
<td></td>
</tr>
<tr>
<td>Etidronate</td>
<td>Didronel (Proctor and Gamble, Cincinnati, Ohio)</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>Skelid (Sanofi Aventis, Bridgewater, New Jersey)</td>
</tr>
</tbody>
</table>

This led to further discoveries through in vivo and in vitro laboratory studies, with much of it led by researchers at Merck Research Laboratories (Whitehouse Station, New Jersey). Sato et al, using rat models, showed the localised specificity of alendronate. They noted the ability of alendronate not only to incorporate specifically into rat bone, but to localise its action via osteoclast activation and subsequent inhibition of bone resorption without osteoclast destruction. Confirming these findings, Masarachia et al noted the propensity of alendronate for osteoclasts over osteoblasts at a ratio of 11:1. In addition, they showed the presence of alendronate deep within the mineralised matrix. Here the drug lies in an inactive state covered by newly formed bone. Deep in the bone, the drug remains dormant, activated only in the presence of osteoclasts to inhibit bone resorption. With promising in vivo and in vitro animal studies, the next step was to determine the mechanism of action at the molecular level. It was shown that alendronate had a considerable inhibitory effect on tyrosine phosphatase, an enzyme that is important in the regulation of osteoclast formation and function. More specifically, it was further suggested that alendronate specifically inhibits farnesyl diphosphate (FPP) synthase, a tyrosine phosphatase, integral to the formation of geranylgeraniol, an intermediate found in the melavonate pathway, which not only regulates osteoclast function and survival, but is also involved in cholesterol synthesis (Fig. 1). This mode of osteoclast inhibition, however, is specific to one of two bisphosphonate subclasses, those containing a nitrogen side chain moiety. With further structural refinement leading to the creation of more bisphosphonate analogues, two subclasses, nitrogen containing (N-BP) and non-nitrogen containing bisphosphonates (n-BP), were subsequently developed (Table I). While the N-BP subclass (alendronate, ibandronate, pamidronate, risedronate, and zoledronate), induces osteoclast inhibition via the melavonate pathway, the n-BP subclass (etidronate, tiludronate) effect bone resorption through its metabolites, which were found to form toxic ATP analogues, inducing osteoclast apoptosis. Through these two pathways, bisphosphonates produce their beneficial clinical effect.

Clinical efficacy of bisphosphonate therapy: FIT, FLEX and HORIZON

In 1995, worldwide, pooled data from two multi-centre, prospective randomised clinical phase III trials offered confirmation of the promise alendronate had shown in previously performed in vitro and in vivo trials. In this phase III clinical trial study, Liberman et al showed consistent, significantly improved bone mineral density (BMD) in the lumbar vertebrae, femoral neck, trochanter and globally throughout the body compared with placebo. During the three-year study period, they also reported a significantly lower incidence of new vertebral fractures, a phenomenon not seen with other forms of treatment. Subsequently, the Fracture Intervention Trial (FIT) Research Group conducted a prospective, double-blind, placebo-controlled randomised, multi-centre clinical trial to assess the efficacy of alendronate on post-menopausal women with low BMD. Enrolling over 6400 women, the FIT trial offered encouraging data. Not only was it effective in maintaining BMD, the drug did so throughout the body, without discriminating between patients at low or high risk for fragility fracture. With increasing follow-up intervals, the FIT data reported sustained BMD increases with a low incidence of adverse side effects, and continued fracture risk reduction. Cost analysis outcomes also increased already high levels of enthusiasm. Chrsichilles et al, analysing the associated economic impact, reported significantly reduced associated healthcare utilisation, reducing costs related to hip fractures by 58% and costs related to fracture care overall by 35%.

With longer follow-up periods leading to additional questions regarding alendronate efficacy after discontinuation, the Fracture Intervention Trial Long-term Extension (FLEX) Research Group was formed. In the FLEX trial, over 1000 women were randomised into either a continued therapy or discontinued therapy (placebo) group and followed for an additional five years follow-up. Not surprisingly, the continued therapy group maintained their BMD and had greater increases in BMD compared with the discontinued therapy group. However, despite the switch to placebo, patients in the discontinued therapy group maintained their reduced level of fracture risk despite slight decreases in BMD, which, of note, still remained above pretreatment levels (Table II). In certain high risk groups, continuation of alendronate in the longer term seemed necessary to achieve persistent non-vertebral fracture prevention.
However promising the results exhibited by alendronate, it was necessary to try and reduce troublesome gastrointestinal side effects while allowing a desirable increase in dosage schedules. With hopes of increasing patient compliance in taking, the bisphosphonates the Health Outcomes and Reduced Incidence with Zoledronic Acid (HORIZON) Pivotal Fracture Trial was conducted in order to assess the efficacy of zoledronic acid, a once-yearly infused N-BP in the treatment of low BMD and fragility fracture prevention. Not surprisingly, the HORIZON Pivotal data exhibited similar data to the FIT and FLEX trials, noting increased BMD and significant fracture risk reduction (Table II). The HORIZON Recurrent trial, which randomised hip fracture patients into zoledronic acid versus placebo groups, also noted significantly lower vertebral and non-vertebral fracture rates, significant fracture risk reduction, and significantly lower associated mortality (Table II). Although avoiding the gastrointestinal side effects seen with zoledronate’s oral counterparts, significantly higher rates of atrial fibrillation caused early concern. However, in a subsequent study, performed by Lyles et al., an association with increased rates of atrial fibrillation was not confirmed. Offering fracture prevention with a once-yearly dosage schedule, zoledronic acid added another option for clinicians, this time hopefully with increased adherence to the medication regimen.

Atypical insufficiency fractures of the femur: controversy and concern
Amidst the enthusiasm surrounding bisphosphonates and their clinical efficacy in preventing fragility fractures, early reports of atypical subtrochanteric fractures potentially related to bone oversuppression caused by this championed drug class seemed counterintuitive. However, beginning with a case report published in 2005, this potential link has become one of the most discussed and controversial orthopaedic topics of recent times.

In 2005, Odvina et al. reported a series of nine patients with spontaneous, atypical fractures, all on bisphosphonate therapy for a period of time ranging from 3 to 8 years. Four patients had fractures in the subtrochanteric region, and each had fractures of the sacrum, rib, ischium, pubic rami and lumbar spine. A total of six out of nine patients had delayed or absent healing during management. While histological analysis showed over suppression of bone turnover, possibly linked to bisphosphonate usage, other factors, such as concomitant treatment with for instance oestrogens and glucocorticoids, left much room for debate.

However, subsequent publications from around the world, spanning several subspecialties, have continued to report these atypical fracture patterns thought to be
associated with long-term bisphosphonate usage (Table II). \cite{14,16,17,58,59} With each new report, certain common radiological and clinical features emerged. Most, if not all, patients had been receiving bisphosphonate therapy for more than five years and had prodromal thigh pain. \cite{14,60,61} Case control studies, both in the orthopaedic and general medical literature, have indicated an increased risk of subtrochanteric fracture, with statistically significant associated long-term bisphosphonate use and specific radiological findings. \cite{3,57,59} Radiologically, physicians began to notice a specific pattern: medial beaking, or cortical hypertrophy of the lateral cortex found within the femoral subtrochanteric region, often bilaterally. \cite{62} Growing concern seemed warranted not only due to the emergence of a consistent clinical presentation, also to the recognition of a new and distinct fracture pattern different from any previously defined in the numerous (15) existing classification systems of subtrochanteric fractures. \cite{63}

However, despite what seems to be an obvious, associated clinical presentation and radiological presentation, the lack of consistent, high-level evidence continued to fuel controversy, especially regarding further management. Some surgeons recommend prophylactic intramedullary nailing in this setting. \cite{14,57,60} Others have recommended

<table>
<thead>
<tr>
<th>Author/s</th>
<th>n</th>
<th>Intervention</th>
<th>Recommendations, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odvina et al \cite{52}</td>
<td>5</td>
<td>Cessation bisphosphonate therapy</td>
<td>Need further studies</td>
</tr>
<tr>
<td>Schneider \cite{53}</td>
<td>1</td>
<td>Intramedullary nail; Cessation bisphosphonate therapy</td>
<td>Consider stopping therapy after several years of use</td>
</tr>
<tr>
<td>Goh et al \cite{57}</td>
<td>9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wennecke et al \cite{55}</td>
<td>1</td>
<td>Bipolar hemiarthroplasty; Teriparatide; Cessation bisphosphonate therapy</td>
<td>Cessation if patient gains achieved response and is at stable plateau</td>
</tr>
<tr>
<td>Kwek et al \cite{16}</td>
<td>17</td>
<td>N/A</td>
<td>Avoid overtreatment; Screen for prodromal symptoms; Consider radiographs to detect early stress reaction; Strongly consider discontinuation upon fracture</td>
</tr>
<tr>
<td>Sayed-Noor and Sjödén \cite{18}</td>
<td>2</td>
<td>Periprosthetic fracture → Non-weight-bearing → Cessation bisphosphonate therapy → reduction internal fixation (ORIF); Intramedullary nail</td>
<td>Radiographs if prodromal symptoms; Consider cessation if early fracture signs; Need further studies</td>
</tr>
<tr>
<td>Capeci and Tejwani \cite{14}</td>
<td>7</td>
<td>Cessation bisphosphonate therapy (after second fracture); Intramedullary nails (four prophylactic)</td>
<td>Investigate new onset thigh/hip pain with radiographs; Cessation bisphosphonate therapy, if atypical pattern suspected, with endocrine consult; Need further studies to assess association and criteria for prophylactic surgical intervention</td>
</tr>
<tr>
<td>Yoon et al \cite{60}</td>
<td>1</td>
<td>Prophylactic bilateral intramedullary nails; Cessation bisphosphonate therapy</td>
<td>Consider prophylactic surgical fixation; Consider cessation bisphosphonate therapy; Need further studies to assess association and criteria for prophylactic surgical intervention</td>
</tr>
<tr>
<td>Das De et al \cite{56}</td>
<td>12</td>
<td>5 Dynamic condylar screw; 1 Angled blade plate; 6 Intramedullary nails</td>
<td>Recommend intramedullary device; Cessation bisphosphonate therapy; Consider anabolic agent; Serial assessment with Fracture Risk Assessment Tool (FRAX); Monitor contralateral femur, prophylactic surgery if indicated; Need further studies</td>
</tr>
<tr>
<td>Sellmeyer \cite{54}</td>
<td>1</td>
<td>Intramedullary rod; Cessation bisphosphonate therapy; Teriparatide</td>
<td>Consider medication holidays for patients on bisphophonate therapy &gt; 5 years; Identify/screen high risk patients (prodromal thigh pain, long-term use); Consider teriparatide; Need further studies</td>
</tr>
</tbody>
</table>
considering ceasing treatment for those patients with a stable BMD who have been on bisphosphonates for more than five years. However, with the lack of evidence, the FDA has only recommended extensive discussion and continued drug usage with strict surveillance.

Further fuelling the controversy is the lack of a direct link between bisphosphonates causing these types of fracture and the clinical presentation. Sellmeyer recently suggested a link between prolonged resorptive suppression and the creation of microdamage to the underlying bony architecture. Accumulated skeletal microdamage, he noted, caused by increased suppression of bone resorption, could lead to increased fragility. Histological data did not provide strong support for that theory, although it is important to note the study was done in patients who had received just three years of treatment. Repeating the study in a population with a much longer period of bisphosphonate therapy could prove more fruitful. Perhaps even more interesting was the uncertainty expressed in a 2004 commentary written by Rodan et al (Merck Laboratory) regarding the potential for fragility caused by microdamage due to prolonged bony suppression, subsequently calling for more animal models to help produce a definitive answer.

Post-hoc analysis of the FIT, FLEX, and HORIZON trials performed by Black et al attempted to clarify such an association. Retrospectively reviewing 284 records of a total of 14195 women, the authors could not find a significant increase in subtrochanteric fractures when compared to placebo. However, with wide confidence intervals, an underpowered statistical analysis was noted, creating the inability to either confirm or deny an obvious link between the atypical fractures and long-term bisphosphonate use.

More recent epidemiological studies, however, have again added support to the association between long-term bisphosphonate usage and atypical subtrochanteric fracture. Abrahamsen, Eiken and Eastell in a national-registry cohort analysis found an increased incidence of subtrochanteric fractures amongst bisphosphonate users, but failed to find a dose-response relationship. In a similar epidemiological analysis conducted at the National Institute of Arthritis, Musculoskeletal and Skin Diseases, a notable increase in the incidence of subtrochanteric fracture was noted, with increasing bisphosphonate usage, despite decreasing overall hip fracture rates. Wang and Bhattacharyya also found that with a reduction of 100 in the number of typical femoral neck or intertrochanteric fractures, there was a subsequent increase of one subtrochanteric fracture. Trying to improve upon the post-hoc analysis performed by Black et al, Park-Wyllie et al performed a population-based, nested case-control study, identifying patients with subtrochanteric or femoral shaft fractures via diagnostic code, and subsequently stratifying and comparing those on with those not on bisphosphonate therapy. The authors concluded that for those women taking the drug for more than five years there was a significantly increased risk of subtrochanteric or femoral shaft fracture, albeit at a low absolute risk when compared to non-bisphosphonate users.

However, specifically regarding the epidemiological and case-controlled studies performed by Abrahamsen et al, Wang and Bhattacharyya and Park-Wyllie et al it is important to note that despite large, population-based cohorts, specific radiological delineations between typical and atypical subtrochanteric fractures were not made. Thus, it is difficult to assess the true increase in the prevalence of atypical fractures, from these studies. More recently, however, Schilcher, Michaelsson and Aspenberg, studying the Swedish National Registry, performed a similar epidemiological analysis, however, with specific radiological identification of those with atypical subtrochanteric fractures. The authors, despite reporting high prevalence of atypical fractures amongst bisphosphonate users, offered encouragement, reporting an absolute risk of 5 per 10000 patient-years when compared with non-bisphosphonate users.

**Future directions and conclusion**

With controversy potentially affecting millions of bisphosphonate users, ongoing FDA investigations, clinical and basic science research initiatives are of paramount importance. A recent task force assembled by the American Society of Bone and Mineral Research (ASBMR) offered several important initiatives that may help to identify epidemiological patterns in order to obtain the true prevalence of these fracture patterns. Creation of specific coding parameters along with an international database included strategies to
identify and tackle this difficult task. While concrete, evidence-based recommendations could not be provided, strict surveillance, overall awareness of prodominal thigh pain, radiological findings, and bisphosphonate usage records were recommendations for prevention (Table III). Proper orthopaedic referrals and fracture stabilisation, along with consideration of periods of not taking the drugs and prophylactic surgery for incomplete fractures, were also recommended. Following through with these initiatives should help in determining the link between these atypical fractures and bisphosphonate usage. Until then, however, surveillance, discussions with patients, and being aware of the possibility of this rare but important adverse event will have to remain at the forefront in order to maintain the great track record put forth by such a revolutionary class of drug.

Supplementary material
A table detailing the major clinical findings from the Fracture Intervention Trial (FIT), Fracture Intervention Trial Long-term Extension (FLEX) and Health Outcomes and Reduced Incidence with Zoledronic Acid (HORIZON) clinical trials is available with the electronic version of this paper on our website at www.jbjs.org.uk

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References


