Diphosphonates are among the many commonly prescribed drugs for osteoporosis management. These synthetic analogues of physiologically occurring inorganic pyrophosphate bind to the hydroxyapatite crystals of bone. Diphosphonates act by decreasing the amount of osteoclast-mediated bone resorption by inducing apoptosis and disrupting the mevalonate biosynthetic pathway. Prospective clinical trials have shown that diphosphonates increase bone mineral density and reduce the risk of fracture. Diphosphonates are generally well tolerated, with a low incidence of side effects. They may be administered orally or intravenously; infusions are the most potent. Few studies have directly studied the effect of diphosphonates on the rate of fracture or time to union. Concern exists regarding the long-term safety of diphosphonates, particularly in patients with osteoporosis. New evidence suggests that long-term therapy may increase the risk of fracture of the femoral shaft, with possible morphologic and prodromal warning signs. Further prospective research into the consequences of diphosphonate-mediated suppressed bone turnover is needed to elucidate a safe duration of treatment.
stream, diphosphonates demonstrate an affinity for bone.

Diphosphonates can be classified in two general categories: simple diphosphonates and aminodiphosphonates (Figure 1), or first- and second-generation diphosphonates, respectively. Aminodiphosphonates are 10 to 10,000 times more potent than simple diphosphonates in inhibiting osteoclastic resorption of bone.\(^1\) Aminodiphosphonates contain an amino group on \(R_2\), with ring-structured amino groups yielding much greater potency than simple amino groups. For example, zoledronate is 20,000 times more potent per equivalent dose than etidronate, the original non-aminodiphosphonate. It appears that these two classes of drug affect osteoclastic resorption of bone in different ways. Simple diphosphonates act by being metabolized into nonhydrolyzable adenosine triphosphate analogues. These metabolites accumulate within osteoclasts, inhibiting cellular metabolism, leading to apoptosis and cell death\(^1\) (Figure 2, A). Aminodiphosphonates appear to act primarily by disrupting the mevalonate biosynthetic pathway. The mevalonate pathway is responsible for cholesterol production and is perhaps best known as a target for common cholesterol-lowering statins. Aminodiphosphonates act by inhibiting protein prenylation, which causes loss of the ruffled border and results in apoptosis\(^2\) (Figure 2, B). The primary target appears to be farnesyl pyrophosphate synthase, although other enzymes may also be affected.

The selectivity of diphosphonates is a function of their affinity to bone rather than to their specific intracellular activity. Diphosphonates bind to hydroxyapatite crystals in bone.\(^3\) They are not integrated directly into hydroxyapatite but rather bind to the surface of the crystal and are then trapped as new crystals form. Diphosphonates have been shown to accumulate at the site of bone resorption where bone mineral is most exposed.\(^4\) As activated osteoclasts resorb bone, the deposited diphosphonate is released into the local microenvironment and is preferentially taken up by osteoclasts. Once internalized, diphosphonates inhibit bone resorption and eventually induce apoptosis.\(^5,6\) Approximately 50% to 80% of diphosphonates are cleared...
from the blood stream by renal excretion, and approximately 1% are cleared through biliary excretion. The remainder of the drug is incorporated into the crystalline structure of bone and may persist for the lifetime of the patient, with an estimated half-life in bone of 10 years.

Dosage and Side Effects

Diphosphonates can be administered either orally or intravenously. Oral bioavailability is poor; only 1% to 5% of the drug is absorbed. Diphosphonates should be taken with water on an empty stomach, and the patient should remain upright for 2 to 3 hours to minimize the risk of esophagitis. Dosage and frequency of administration vary by drug, with daily, weekly, and monthly dosing schedules. Typical regimens are presented in Table 1.

Diphosphonates are generally well tolerated, with a low incidence of side effects. Upper gastrointestinal side effects have been reported, including dyspepsia, dysphagia, esophagitis, and esophageal ulcers. Symptomatic hypocalcemia has been reported in patients with hypoparathyroidism and vitamin D deficiency. Ocular side effects, including pain, blurred vision, scleritis, and uveitis, have also been reported with diphosphonate use. There are sporadic reports of myalgia and arthralgia in patients on diphosphonate therapy. Osteonecrosis of the jaw is a rare complication of diphosphonate therapy. Reports of "phossy jaw" date as far back as the mid 19th century in factory workers exposed to white phosphorus. The incidence of jaw osteonecrosis is approximately 1 in 50,000 patient-years when oral diphosphonates are taken for osteoporosis. The risk of osteonecrosis is higher in oncology patients, patients undergoing chemotherapy, and patients undergoing significant dental procedures. This complication may be dose-specific; oncology patients typically receive much higher doses of diphosphonates than do those treated for osteoporosis.

The mechanisms involved in necrosis of the jaw bones are poorly understood, but several theories exist. The unique environment of the oral cavity normally facilitates quick and uncomplicated healing after a surgical insult, such as tooth extraction. When this environment is disturbed, however, either by loss of vascularization of the jawbones from tumoricidal radiation or some other agent or pathology, then minor injury may increase the risk of osteonecrosis and possible secondary osteomyelitis. The mandible and maxilla are also sites of high bone turnover, so the possibility exists that diphosphonates are selectively deposited in jawbones more than in other bony tissues. However, we are unaware of any study demonstrating selective increase in diphosphonate deposition in certain bones, such as the jaws. Another possibility is that other concomitant medications may exacerbate wound healing problems and could be considered to be possible cofactors.

Infusion reactions have been reported with the use of zoledronic acid.

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Yearly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate&lt;sup&gt;a&lt;/sup&gt; (Didronel [Procter &amp; Gamble Pharmaceuticals, Cincinnati, OH])</td>
<td>5 mg/kg PO</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tiludronate&lt;sup&gt;a&lt;/sup&gt; (Skelid, sanofi-aventis, Bridgewater, NJ)</td>
<td>400 mg PO</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pamidronate&lt;sup&gt;c&lt;/sup&gt; (Aredia [Novartis Pharmaceuticals, Basel, Switzerland])</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>30-90 mg infusion</td>
</tr>
<tr>
<td>Alendronate&lt;sup&gt;a,c&lt;/sup&gt; (Fosamax, Fosamax Plus D [Merck, Whitehouse Station, NJ])</td>
<td>10 mg PO</td>
<td>70 mg PO</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ibandronate&lt;sup&gt;c&lt;/sup&gt; (Boniva [Roche Laboratories, Nutley, NJ])</td>
<td>2.5 mg PO</td>
<td>—</td>
<td>150 mg PO</td>
<td>—</td>
</tr>
<tr>
<td>Risedronate&lt;sup&gt;a,c&lt;/sup&gt; (Actonel, Actonel with Calcium [Procter &amp; Gamble])</td>
<td>5 mg PO</td>
<td>35 mg PO</td>
<td>150 mg PO</td>
<td>—</td>
</tr>
<tr>
<td>Zoledronic acid&lt;sup&gt;c&lt;/sup&gt; (Reclast, Zometa [Novartis])</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4-mg infusion</td>
</tr>
</tbody>
</table>

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<sup>a</sup> US FDA approved in the treatment of Paget disease of bone<br>
<sup>b</sup> US FDA approved in the treatment of skeletal metastatic disease<br>
<sup>c</sup> US FDA approved in the treatment of osteoporosis
acid and pamidronate. Symptoms include low-grade fever, myalgia, arthralgia, and malaise persisting for 24 to 72 hours following drug administration. As many as 32% of patients may experience such symptoms following the first infusion, with reduced incidence following subsequent infusions. Zoledronic acid has also been associated with a slight increase in the risk of atrial fibrillation. The US FDA issued an alert in 2008 regarding the association between diphosphonate use and transient musculoskeletal pain, which may occur days, months, or years after therapy is begun. This phenomenon is distinct from acute infusion response, whose frequency and contributing risk factors between severe musculoskeletal pain and diphosphonate use are currently unknown.

Analysis of human iliac crest biopsies suggests that microdamage will accumulate after 5 years of alendronate therapy, particularly in patients with low bone mineral density (BMD). Microdamage is generally defined as matrix failure detectable with light microscopy. This likely begins with debonding of the collagen fiber matrix, progressing through the hierarchy of bone architecture until very fine cracks coalesce into dye-penetrable cracks that are visible under a light microscope. The cracks may also compound upon one another, changing the stress state to produce more and larger cracks. Some authors advise checking markers of bone metabolism in patients taking diphosphonates and considering a drug holiday if turnover has stopped. Markers of bone resorption seem to be stronger predictors of future bone loss than are markers of bone formation; these markers are correlated more strongly in elderly women than in younger women. Currently available markers of bone resorption include pyridinoline, deoxypyridinoline, N-telopeptides of type 1 collagen, and C-telopeptides of type 1 collagen. Pyridinolines are measured in urine, whereas telopeptides can be measured in urine or serum. The advantage of using bone markers instead of BMD to assess bone turnover is that significant changes in bone markers can be observed at 3 to 6 months after the start of therapy, whereas significant BMD changes may take 18 months to materialize.

Currently there is no consensus on how long to continue diphosphonate therapy. However, stopping therapy after 5 years may be reasonable for some patients because there appears to be a residual benefit on BMD and fracture prevention for up to 5 years following cessation of therapy. This was demonstrated in the Fracture Intervention Trial Long-Term Extension (ie, FLEX), a study involving 1,099 postmenopausal women who had previously undergone alendronate therapy for 5 years.

Reduction in Risk of Osteoporotic Fracture

Several prospective randomized clinical trials have shown that diphosphonates, including alendronate, risedronate, ibandronate, and zoledronic acid, increase BMD and decrease the risk of fragility fracture. Alendronate was the first orally activeaminodiphostonate available in the United States. Its effectiveness in reducing the incidence of osteoporotic fractures was investigated in the Fracture Intervention Trial (FIT), which involved 2,027 women with low BMD in the femoral neck, with or without vertebral fracture. Patients were randomized to receive alendronate or a placebo for 3 years. Clinically and radiographically evident vertebral fractures served as the primary end point. Fifteen percent of patients in the placebo group sustained vertebral fracture, versus 8% in the alendronate group—a 47% lower risk \( (P = 0.001) \). Additionally, the incidence of any clinical fracture was lower in the alendronate group than in the placebo group (13.6% versus 18.2%, respectively), and patients in the alendronate group had fewer hip and wrist fractures than did those in the placebo group. In a 10-year extension of the study published by Bone et al, treatment with 10 mg alendronate daily resulted in a significant increase in BMD in the lumbar spine as well as at other skeletal sites. The reduction in fracture risk appears to be most pronounced in patients with osteoporosis.

Liberman et al found that alendronate therapy of 10 mg/d increased bone density of the spine and proximal femur by 8.8% and 7.8%, respectively, over a 3-year period compared with placebo \( (P < 0.001) \). Recent meta-analyses of both alendronate and risedronate therapy in postmenopausal women demonstrated a low relative risk of vertebral and non-vertebral fracture. Zoledronic acid has also been shown to decrease the rate of fragility fracture and mortality compared with placebo. In a benchmark randomized, double-blind, placebo-controlled trial, 2,127 patients were assigned to receive yearly zoledronic acid infusion or placebo. Administration of a single intravenous dose of zoledronic acid within 90 days following hip fracture resulted in a 35% reduction in the incidence of second fracture. A 28% reduction in deaths from any cause was seen in the zoledronic acid group, and no cases of osteonecrosis of the jaw or adverse effects on fracture healing were noted.

These data collectively demonstrate the utility of diphosphonate therapy in reducing the risk of osteoporotic fractures and subsequent mortality, most notably from hip fracture. The significance of this cannot be overstated.
Diphosphonates and Fracture Healing

There is concern that diphosphonates may hamper the normal healing process following fracture; however, there is a paucity of studies directly examining the effect of diphosphonates on the rate of or time to union in fracture patients. Munns et al\(^\text{33}\) reported that pamidronate treatment was associated with delayed healing after osteotomy but not after fracture in children with moderate to severe osteogenesis imperfecta. Adult studies are lacking. Animal studies have shown that the effect of zoledronic acid on fracture repair is characterized by a larger trabecular bone volume, increased callus size and bone mineral content, and improved mechanical strength.\(^\text{30,31}\) However, a delay in remodeling of the hard callus during endochondral fracture repair was observed.\(^\text{30,31}\)

Recent studies have provided evidence that diphosphonates stimulate the proliferation of osteoblasts and osteoblast-like cells. They enhance the proliferation of bone marrow stromal cells and promote osteoblastic differentiation, primarily mediated through bone morphogenetic protein-2.\(^\text{32}\) Diphosphonates may also prevent osteoblast apoptosis through an unknown mechanism, thereby indirectly contributing to the relative increase in active cell numbers.

Primary bone healing is dependent on osteoclast function at the leading edge of cutting cones to cross the fracture site. There are no clinical data to support or refute the use of diphosphonates in this setting. Further research into the effects of diphosphonates on primary bone healing is required, although indirect evidence suggests that diphosphonates are safe to use following surgical fixation of fractures. Data from animal studies have demonstrated a delay in union following spinal fusion while the animals were on diphosphonates.\(^\text{33}\) The proper dose and timing of administration during the postoperative period following fracture or spinal fusion remains to be defined.

Diphosphonates and Total Joint Arthroplasty

Data regarding the use of diphosphonates in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) are limited. Periprosthetic bone loss after THA and TKA is thought to occur primarily because of a stress-shielding phenomenon. Bone surrounding the new joint adjusts its mineral density and structure to meet the changed mechanical demands. Local surgical trauma and immobilization can also negatively affect bone quality. Poor bone density and structure around the implant may place the recipients of these implants at greater risk of aseptic loosening and periprosthetic fracture. There is some evidence that patients on diphosphonate therapy may have a lower incidence of these postoperative complications after THA or TKA.

In a randomized controlled trial of 19 patients with TKA, patients who took alendronate and calcium were found to maintain distal femoral BMD values close to baseline values, whereas patients who received only calcium showed significant bone loss at 1-year follow-up.\(^\text{34}\) Bhandari et al\(^\text{35}\) conducted a meta-analysis of six randomized controlled trials and found that diphosphonates have a beneficial effect in maintaining periprosthetic BMD compared with controls. Friedl et al\(^\text{36}\) randomized patients undergoing cementless THA to receive either a single infusion of zoledronic acid or placebo. They demonstrated a statistically significant reduction in acetabular component subsidence (\(P < 0.05\)) and a trend for less femoral subsidence in patients treated with zoledronic acid. Neither acetabular or femoral failure of ingrowth was observed.

Diphosphonates and Femoral Shaft Stress Fracture

Recent case series have implicated diphosphonate therapy—specifically, alendronate—with low-energy fractures of the subtrochanteric region of the femur. The earliest report of fractures associated with alendronate use was by Odvina et al\(^\text{37}\) in 2005. They reported a series of nine spontaneous fractures of the pelvis, femur, and sacrum. More recent series focus specifically on fractures of the femoral shaft, particularly in the subtrochanteric region.\(^\text{38,39}\)

Goh et al\(^\text{38}\) and Neviaser et al\(^\text{39}\) presented case series of 13 and 70 patients, respectively, who sustained subtrochanteric femur fractures. A high proportion of patients treated with alendronate had a cortical beak on the anterolateral aspect of the femur (Figure 3). The cause and importance of this abnormality is unknown. Five of the 13 patients in the study by Goh et al\(^\text{38}\) recalled prodromal pain prior to their fractures.

In a case-control study, Lenart et al\(^\text{40}\) linked long-term diphosphonate use with insufficiency fractures of the femur in postmenopausal women. Diphosphonate use was observed in 15 of the 41 cases of subtrochanteric/shaft fracture, compared with 9 of the 82 intertrochanteric/femoral neck controls. The beaking pattern was identified ra-
diographically in 10 of the 15 subtrochanteric/shaft cases managed with a diphosphonate.

Animal studies suggest that prolonged diphosphonate use may lead to the accumulation of microdamage over time and that high doses of diphosphonate are associated with weakened mechanical properties of bone. Diphosphonate-mediated turnover suppression in a canine model was associated with a four- to sevenfold increase in microdamage and a 20% to 40% reduction in energy to fracture. However, the normal rate of turnover in the human femoral shaft is low (<3% per year), and it seems implausible that a further reduction in this turnover rate could be solely responsible for the increased fracture risk.

Glycation of bone tissue has also been implicated as a potential cause of femoral shaft fracture. As bone tissue ages, the bone accumulates products of processes leading to non-enzymatic glycation of the bone tissue, or advanced glycation end products. Glycation of bone tissue has been shown to make bone more brittle, with a decrease in the deformability of bone before fracture. Animal models suggest that there is an accumulation of advanced glycation end products in cortical and trabecular bone with diphosphonate therapy. Glycation of bone is a common problem in persons with diabetes and is one reason for the increased risk of fracture in persons with type II diabetes, despite normal BMD levels.

The aforementioned cases series have been refuted by a recent study of the Danish National Hospital Register. Abrahamsen et al could find no data in this large registry study to support the conclusion that long-term alendronate use was responsible for an increase in the rate of atypical femur fractures. However, this study was based on discharge diagnoses and did not include direct patient or radiographic evaluation.

Large-scale randomized controlled trials demonstrate a decrease in overall fracture risk; however, most of these studies are of <5 years duration. It is possible that longer-term use of diphosphonates may lead to an increased risk of fracture. Without the extension of previous studies or the undertaking of a direct observational study, the nature and magnitude of this potential risk will remain unknown.

Summary

Diphosphonates are among the most commonly prescribed treatments for osteoporosis. They have been shown to increase BMD over time and reduce the rate of fragility fractures. In general, this class of medication is well tolerated, with few side effects. Further study is necessary to determine proper dosing regimens following surgical fixation of fractures. Diphosphonate use appears to be safe in patients undergoing cementless total joint arthroplasty, although detailed studies are lacking. Recent case series suggest a possible association between long-term diphosphonate therapy and the development of stress fractures of the femoral shaft, and the optimum duration of therapy remains unclear. Direct study into the mechanism of this association as well as the magnitude of the clinical problem is required to obtain a clear picture of this emerging concern.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 9, 20-28, 35, and 36 are level I studies. References 10, 19, and 34 are level II studies. References 17, 29, and 40 are level III studies. References 11,
37-39, and 45 are level IV studies. References 12, 14, 15, and 18 are level V expert opinion.

Citation numbers printed in bold type indicate references published within the past 5 years.


