

CLINICAL THERAPEUTICS

Bisphosphonates for Osteoporosis

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A 67-year-old woman was referred by her primary care physician for treatment of osteoporosis and progressive bone loss. One year before the visit, the patient had discontinued hormone-replacement therapy. She had subsequently begun to experience midback pain and lost 3.8 cm (1.5 in.) in height. A dual-energy x-ray absorptiometry (DXA) scan showed bone mineral density T scores of -3.1 at the lumbar spine and -2.8 at the femoral neck, which are consistent with a diagnosis of osteoporosis. One year later, a second scan showed a further decrease of 5.4% in bone mineral density at the lumbar spine (Fig. 1), as well as a compression fracture of the 11th thoracic vertebra (Fig. 2). Results of blood and urine tests ruled out the common secondary causes of osteoporosis. To prevent additional vertebral fractures, oral bisphosphonate therapy was recommended.

THE CLINICAL PROBLEM

Osteoporosis is a systemic skeletal disorder that is characterized by the loss of bone tissue, disruption of bone architecture, and bone fragility, leading to an increased risk of fractures.¹ Bone loss and low bone mass are asymptomatic until fractures occur. Estrogen deficiency after menopause is the most common cause of osteoporosis, but secondary causes² must be ruled out before treatment is undertaken (Table 1).

Osteoporosis is the most common metabolic bone disease and the most common cause of fractures in older adults in the United States. Ten million people in the United States have osteoporosis, and an additional 33 million people have low bone mass (osteopenia) and are at increased risk for fractures.^{4,5} More than 2 million fractures occur each year as a result of osteoporosis or osteopenia, including 300,000 hip fractures, 547,000 vertebral fractures, and 135,000 pelvic fractures. Postmenopausal white women have a 40% lifetime risk of at least one osteoporotic fracture.⁴

Osteoporotic hip fractures are associated with the highest morbidity and mortality. Up to 50% of patients with such fractures have permanently impaired mobility, and 25% lose the skills necessary to live independently.^{6,7} A recent meta-analysis showed that among older men and women, the rate of death from any cause is increased by a factor of 5 to 8 during the first 3 months after a hip fracture.⁸

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Estrogen deficiency due to either spontaneous or surgical menopause⁹ increases the production by bone marrow stromal cells and osteoblasts of the receptor activator of nuclear factor κ B ligand (RANKL), which, in turn, increases the binding of RANKL¹⁰ to the osteoclast cell-surface receptor nuclear factor κ B (RANK). Increased

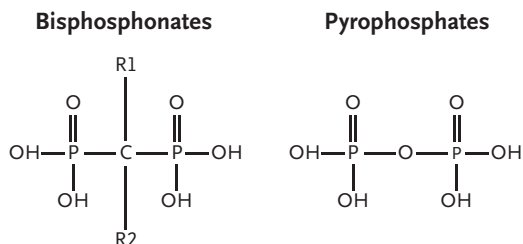
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binding of RANKL to RANK initiates the proliferation of osteoclast precursors and their differentiation into mature osteoclasts.¹⁰⁻¹² The expanded osteoclast population increases bone turnover and the depth and number of resorption pits (Fig. 3). Later in the course of menopause, age-related bone loss and accompanying changes in the properties of bone material exacerbate the bone loss and fragility associated with estrogen deficiency.¹⁰ At the microscopical level, the increased number and activity of osteoclasts disrupt trabecular connectivity and increase cortical porosity.^{9,11} Resorption pits are incompletely filled, since osteoblastic new bone formation does not keep pace with rates of bone resorption.¹⁰ Reduced bone density and bone quality compromise the mechanical weight-bearing properties of the skeleton and confer a predisposition to fractures occurring either spontaneously or when falls cause mechanical overload.¹¹

Bisphosphonates reduce fractures by suppressing bone resorption.^{12,13} The molecular structure of the bisphosphonates (P-C-P) is analogous to that of the naturally occurring pyrophosphates (P-O-P), with two short side chains (R1 and R2) attached to the C core.



The R1 side chain determines bone-binding affinity, and the R2 side chain determines antiresorption potency. Bisphosphonates that are approved for use in the United States (alendronate, ibandronate, risedronate, and zoledronate) have nitrogen-containing R2 side chains¹⁴ that enhance antiresorptive and antifracture potency. Variations in the structure of the side chains determine the strength with which the bisphosphonate binds to bone, the distribution through bone, and the amount of time it remains in the bone after treatment is discontinued.¹⁵

In bone, bisphosphonates accumulate in the hydroxyapatite mineral phase, and the concentration of the bisphosphonates is increased by a factor of 8 at sites of active bone resorption.^{14,16,17} The bound nitrogen-containing bisphosphonates enter osteoclasts and reduce resorption through inhi-

bition of farnesyl pyrophosphate synthase (FPPS), an enzyme in the mevalonate-to-cholesterol pathway.^{18,19} Inhibition of FPPS interferes with isoprenylation of small guanosine triphosphatases (GTPases) at the ruffled border of the osteoclasts and disrupts the attachment of osteoclasts to the bone surface, which stops resorption and promotes early cell death.^{16,20}

CLINICAL EVIDENCE

Three of the most important phase 3 trials of the use of bisphosphonates for the treatment of osteoporosis are described below. In these trials, a reduction in the rate of fractures was the primary end point, and increases in bone mineral density at the lumbar spine and a reduction in markers of bone turnover were secondary end points.

In the Fracture Intervention Trial (FIT),²¹ 2027 postmenopausal women at high risk for fracture, with low bone density at the femoral neck and at least one vertebral fracture, were randomly assigned to either placebo or alendronate, at a dose of 5 mg daily for 24 months, followed by 10 mg daily for the final 12 months of the trial. At 36 months, 15.0% of the women who received the placebo and 8.0% of the women who were treated with alendronate had sustained one or more new vertebral fractures, as assessed by radiography ($P=0.001$). New hip fractures occurred in 2.1% of the women in the placebo group and 1.1% of the women in the alendronate group ($P=0.05$).

In the Vertebral Efficacy with Risedronate Therapy (VERT) trial,²² 2458 postmenopausal women with at least one vertebral fracture and a T score at the lumbar spine of -2.0 or less were randomly assigned to either placebo or risedronate at a dose of 2.5 mg or 5 mg daily. During the course of the trial, data from other studies suggested that a dose of 2.5 mg was less effective than a dose of 5 mg; therefore the 2.5-mg group was discontinued. In the two remaining groups, the rate of new vertebral fractures after 3 years was 11.3% among subjects treated with 5 mg of risedronate daily, as compared with 16.3% in the placebo group ($P=0.003$). In a subsequent trial, risedronate was shown to be effective in reducing the rate of hip fractures as well.²³

The efficacy of zoledronic acid in the treatment of osteoporosis was evaluated in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trial (HORIZON; ClinicalTrials.gov number, NCT00049829).²⁴ In this trial,

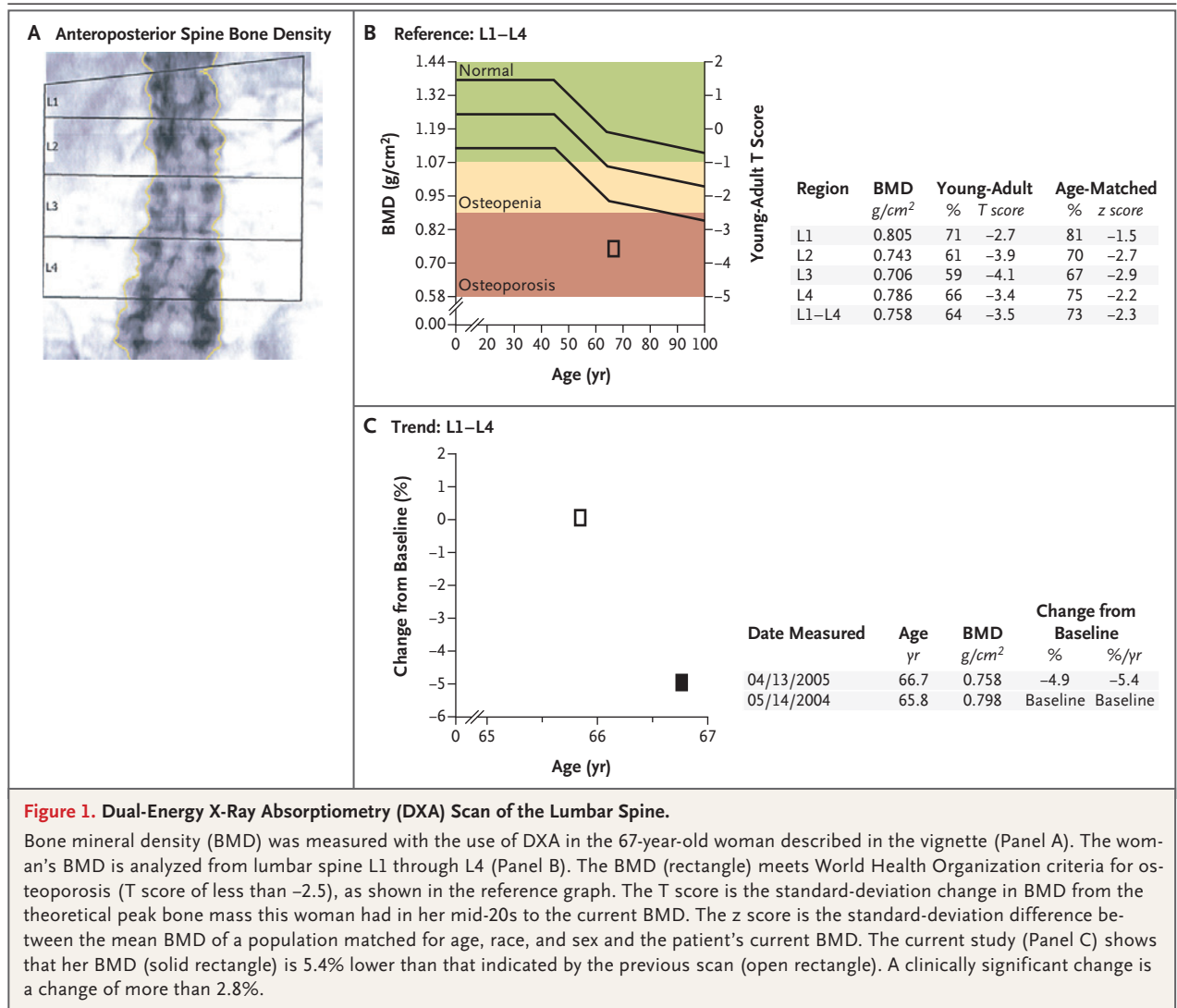


Figure 1. Dual-Energy X-Ray Absorptiometry (DXA) Scan of the Lumbar Spine.

Bone mineral density (BMD) was measured with the use of DXA in the 67-year-old woman described in the vignette (Panel A). The woman's BMD is analyzed from lumbar spine L1 through L4 (Panel B). The BMD (rectangle) meets World Health Organization criteria for osteoporosis (T score of less than -2.5), as shown in the reference graph. The T score is the standard-deviation change in BMD from the theoretical peak bone mass this woman had in her mid-20s to the current BMD. The z score is the standard-deviation difference between the mean BMD of a population matched for age, race, and sex and the patient's current BMD. The current study (Panel C) shows that her BMD (solid rectangle) is 5.4% lower than that indicated by the previous scan (open rectangle). A clinically significant change is a change of more than 2.8%.

7765 postmenopausal women with osteoporosis (T score of -2.5 or less or -1.5 or less with evidence of vertebral fracture) were randomly assigned to either zoledronic acid, at a dose of 5 mg administered at baseline, 12 months, and 24 months, or placebo. At 36 months, the absolute rate of new vertebral fractures as assessed by standard radiography was 3.3% in the zoledronic acid group, as compared with 10.9% in the placebo group (P<0.001). There were 52 new hip fractures (1.4%) in the zoledronic acid group, as compared with 88 (2.5%) in the placebo group (P<0.001).

Randomized, placebo-controlled trials of other oral bisphosphonates, including ibandronate,²⁵ clodronate,²⁶ and etidronate,²⁷ have shown that these drugs also have efficacy in reducing the risk of new vertebral fractures. However, because these

trials were not powered to show efficacy for the treatment of hip fractures, the clinical usefulness of these agents for preventing hip fractures is currently unknown. Pamidronate has been used to treat a variety of bone diseases in children and adults. However, no randomized, placebo-controlled trial has been performed with sufficient power to assess the efficacy of the drug for the treatment of hip fracture in women with postmenopausal osteoporosis.

CLINICAL USE

All postmenopausal women with measurements of bone mineral density at either the spine or the hip that meet World Health Organization (WHO) criteria for osteoporosis (T score of less than -2.5)

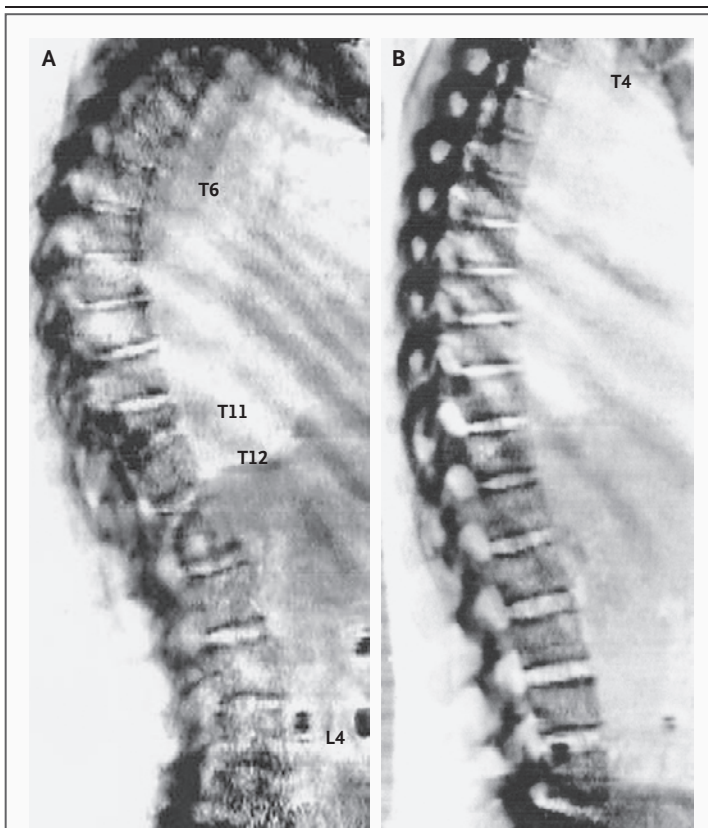


Figure 2. Dual-Energy X-Ray Absorptiometry (DXA) Scan of the Thoracic and Lumbar Spine.

Vertebral deformation at the thoracic and lumbar spine was assessed in the patient described in the vignette, with the use of the vertebral-fracture assessment on the same DXA scanner as that used for the measurement of bone mineral density in Figure 1. Panel A shows thoracic kyphosis due to a 75% loss of height of T11. For comparison, Panel B shows a normal vertebral-fracture assessment in a 58-year-old woman without osteoporosis.

should receive long-term therapy with an agent that has been proven to prevent fractures. In contrast, it may be difficult to decide whom to treat among the large number of patients who have osteopenia (T score of -1.0 to -2.5). Many postmenopausal women in whom fractures develop have osteopenia rather than osteoporosis; in these women, the fractures may occur because of the contributions of risk factors that are independent of bone mineral density.²⁸ I often use the WHO Fracture Risk Assessment Tool (FRAX; www.sheffield.ac.uk/FRAX/) to assist in making treatment decisions. FRAX is a calculator algorithm that incorporates risk factors with measurements of bone mineral density, generating a quantitative estimate of the 10-year probability of a major osteoporotic fracture (hip, vertebral, humerus, or fore-

arm) or of a hip fracture alone in patients who have not yet begun therapy. In general, I initiate pharmacologic treatment in patients who have a 10-year probability of a hip fracture that exceeds 3% or a 10-year probability of a major osteoporotic fracture that exceeds 20%.²⁹

In addition to weighing the objective evidence, I consider the patient's lifestyle. I am more likely to initiate treatment for low bone mass in a patient who wishes to continue participating in sports or recreational activities such as cycling, tennis, skiing, and running. Such patients are likely to have a greater risk of falls and fractures than are sedentary patients.

A major consideration in selecting therapy is the risk of hip fracture. All treatments that have been approved by the Food and Drug Administration (FDA) have shown efficacy in reducing the rates of vertebral fracture, but not all have been clearly shown to reduce the rate of hip fractures. If bone mineral density at the hip is low, I usually select an agent for which there are trials showing efficacy in preventing hip fractures. I recommend either alendronate or risedronate if the patient is capable of taking an oral agent. If the patient cannot tolerate oral bisphosphonates, then I may select intravenous zoledronic acid. If bone density at the hip is normal or only mildly reduced, I may select oral or intravenous ibandronate, which has not been shown to be effective in reducing the risk of hip fracture.

Alternatives to bisphosphonates include the anabolic agent teriparatide (parathyroid hormone 1-34), which reduces the risk of vertebral and nonvertebral fractures but, among subjects in a large, pivotal trial, did not reduce the risk of hip fracture alone.³⁰ Teriparatide is also more expensive than the bisphosphonates and requires daily subcutaneous injection. Estrogen is effective in decreasing the risk of vertebral and hip fractures in postmenopausal women³¹ but may confer increased risks of breast cancer and cardiovascular disease. Raloxifene is an oral selective estrogen-receptor modulator (SERM) that decreases the risk of vertebral fractures by 40 to 49%, but it may not reduce the risk of nonvertebral fractures.³² Calcitonin administered by means of a nasal spray is an antiresorptive agent that has limited efficacy in reducing the risk of vertebral fractures and lacks efficacy in preventing hip fracture.³³

Oral bisphosphonates must be taken after an overnight fast either once weekly (alendronate at a dose of 70 mg or risedronate at a dose of 35 mg),

once monthly (ibandronate at a dose of 150 mg or risedronate at a dose of 150 mg), or on 2 consecutive days once monthly (risedronate at a dose of 75 mg). The tablets are taken with 6 to 8 oz of tap water. The patient should remain upright for at least 30 minutes after taking the drug to minimize gastroesophageal reflux. To optimize absorption, food, medications, and liquids other than tap or filtered water should be avoided for at least 30 to 45 minutes to allow for dissolution of the tablet and gastric emptying.

Intravenous bisphosphonates include ibandronate (at a dose of 3 mg every 3 months) and zoledronic acid (at a dose of 5 mg every 12 months). They are usually administered in an outpatient facility that has the resources for administering and monitoring intravenous infusions.

Oral and intravenous bisphosphonates are contraindicated in patients who have had a prior allergic reaction to a bisphosphonate or who have an estimated creatinine clearance of 35 ml per minute or less, vitamin D depletion (serum 25-hydroxyvitamin D levels should be more than 30 ng per milliliter before initiating bisphosphonates), osteomalacia (vitamin D depletion or deficiency causing defective mineralization), or hypocalcemia. Oral bisphosphonates are contraindicated in patients who have impaired swallowing or esophageal disorders such as achalasia, esophageal varices, or severe gastroesophageal reflux or who are unable to sit up for at least 30 minutes after taking the medication. There are no known interactions between bisphosphonates and other medications.

After initiating bisphosphonate therapy, I typically reevaluate the patient in 1 month to assess tolerance and thereafter at 3 months, 6 months, and 1 year. At 3 months and 6 months, I obtain measurements of bone-turnover markers, such as osteocalcin or serum C-terminal telopeptide of type 1 collagen (CTX). At 1 year, and every 2 years thereafter, I repeat the assessment of bone mineral density with the use of DXA. An increase in bone mineral density is not required for a therapy to be considered effective, but a substantial decline in bone mineral density requires further evaluation.

Poor adherence to therapy should be suspected if the patient has an otherwise unexplained decline in bone mineral density, a new fracture, continued bone loss, or high rates of bone turnover that persist after 12 months of therapy. When I suspect poor adherence, I ask the patient wheth-

Table 1. Common Secondary Causes of Osteoporosis and Laboratory Evaluations.*

Possible Cause of Osteoporosis	Laboratory Test
Vitamin D deficiency	Measurement of serum 25-hydroxyvitamin D level
Primary hyperparathyroidism	Measurement of fasting serum calcium and parathyroid hormone levels
Celiac disease	Measurement of serum tissue transglutaminase, total IgA, and gliadin levels
Idiopathic hypercalciuria	Measurement of 24-hour urine calcium excretion after discontinuation of calcium supplements
Hyperthyroidism	Measurement of serum thyrotropin and total thyroxine levels
Myeloma	Serum and urine immunoelectrophoresis

* Additional information regarding secondary causes of osteoporosis can be found in Tannenbaum et al.² and Jamal et al.³

er he or she has had any side effects and attempt to document the patient's use of the drug by measuring markers of bone turnover. Evidence of treatment failure in a patient with good adherence to an oral bisphosphonate regimen requires a change to either intravenous zoledronic acid or another class of medications such as anabolic agents (e.g., teriparatide).

The optimal duration of bisphosphonate therapy remains unresolved. However, on the basis of available data, it seems likely that discontinuing therapy after 5 years, at least for a temporary drug holiday, is not harmful and may be advantageous.³⁴ Patients with mildly reduced bone mineral density may be the most suitable candidates for a 1-year to 2-year drug holiday, because the risk of fracture will be low if bone loss occurs while the person is not receiving therapy.

Generic alendronate was introduced in 2008 and is less expensive than other agents, with cost ranging from \$4 to \$40 per month. The cost of risedronate ranges from \$60 to \$120 per month; generic risedronate will become available in the near future. The cost of oral ibandronate ranges from \$90 to \$130 per month. One infusion of zoledronic acid is estimated to cost \$1,300; intravenous ibandronate costs about \$1,300 per year.

ADVERSE EFFECTS

An acute-phase reaction characterized by fever, myalgia, bone pain, and weakness³⁵ occurs in 20% of patients after an initial intravenous infusion of

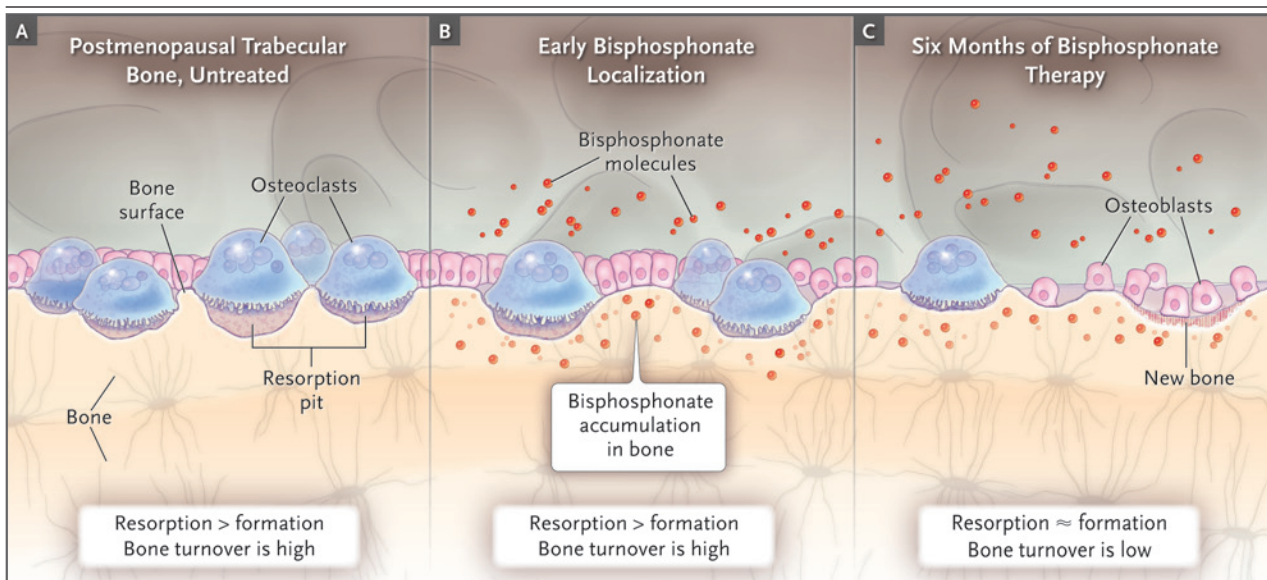


Figure 3. Cellular Elements Involved in Postmenopausal Trabecular Bone Turnover before and during Bisphosphonate Therapy.

Panel A shows the untreated postmenopausal state, in which osteoclast-mediated bone resorption occurs at a high rate, exceeding osteoblast-driven bone formation and leading to net bone loss. Panel B shows the initial events associated with bisphosphonate therapy, including the localization and concentration of bisphosphonates in bone through binding to sites of active bone resorption. Panel C shows the effects of bisphosphonates after 6 months of therapy. The number of osteoclasts has decreased owing to early apoptosis. As a result, bone resorption is decreased, and osteoblasts and bone formation are also decreased. The bisphosphonate concentration is reduced around previous resorption pits. A lower steady-state rate of bone turnover, similar to premenopausal rates, is established.

bisphosphonates and in a very small number of patients during oral therapy. Erosive esophagitis, ulceration, and bleeding have been associated with daily oral alendronate or risedronate therapy but occur rarely with current (nondaily) regimens. Heartburn, chest pain, hoarseness, and vocal-cord irritation³⁶ may occur with weekly (alendronate or risedronate) or monthly (ibandronate or risedronate) therapy. A relationship between esophageal cancer and oral bisphosphonates, suggested on the basis of a small number of case reports, has not been substantiated.³⁷

Transient renal toxic effects can occur after rapid intravenous administration.^{38,39} Slow infusion rates (no less than 15 minutes) and lower doses minimize peak drug serum levels and the risk of renal damage. Bisphosphonates are not recommended when creatinine clearance is less than 35 ml per minute.³⁸ Dose reductions may be required for patients with stage III chronic kidney disease (as defined by an estimated glomerular filtration rate between 59 and 30 ml per minute per 1.73 m² of body-surface area). Mild transient hypocalcemia is a rare complication of intrave-

nous bisphosphonate therapy that may require an interruption in treatment,⁴⁰ but once the serum calcium level has returned to the normal range, therapy can be resumed. Severe hypocalcemia is a contraindication for continued administration.

Osteonecrosis of the jaw is a rare but serious complication of long-term bisphosphonate therapy that may appear either spontaneously or after an oral surgical procedure. Exposed mandibular or maxillary dead bone, nonhealing mucosa, and chronic infection may persist for weeks to years.⁴¹⁻⁴³ More than 95% of cases of osteonecrosis of the jaw occur in patients who are receiving zoledronic acid or pamidronate for the treatment of myeloma, breast cancer, or other bone cancers at doses 10 to 12 times as high as those used for the treatment of osteoporosis.^{42,44}

Case reports suggest that atypical femoral fractures (in the subtrochanteric and mid-diaphyseal portions of the femur) may be more common during bisphosphonate therapy.^{37,45} Recent data from a cross-sectional study of femur fractures recorded in the Danish national health registry⁴⁶ and a pooled post hoc analysis of the trials that

studied the effects of alendronate and zoledronic acid on the incidence of fractures⁴⁷ showed no relationship between the use of bisphosphonates and atypical femur fractures. However, these reports are not definitive, and the possibility of a relationship continues to be investigated.

AREAS OF UNCERTAINTY

The optimal duration of bisphosphonate therapy remains uncertain. Recent retrospective studies and case reports suggest that long-term bisphosphonate therapy may result in the suppression of bone turnover and confer a predisposition to increased bone fragility, with an increased risk for atypical femur fractures.³⁷ Markers of bone turnover underestimate the extent of suppressed bone formation,^{12,48} and their usefulness in monitoring long-term safety may therefore be limited. An accumulation of microcracks in bone-biopsy specimens was found in one study of patients receiving alendronate therapy when the analysis was adjusted for potential confounders such as age and bone mineral density at the femoral neck⁴⁹ but not in another study of long-term alendronate therapy (mean, 6.5 years).⁵⁰ Prospective studies are needed to estimate the long-term risk of side effects associated with bisphosphonate therapy, including osteonecrosis of the jaw and atypical femur fractures. Until a better estimate of the risk of these complications emerges, one must balance the long-term risk of these uncommon complications against the known efficacy of the agents in reducing rates of common osteoporotic fractures. It is also not known whether these complications can be minimized by periodic rotation of treatment from one class of agents to another.

GUIDELINES

Guidelines for the management of osteoporosis published by the National Osteoporosis Foundation,⁵¹ the American Association of Clinical Endocrinologists,⁵² the American College of Physicians,⁵³ the American College of Obstetricians and

Gynecologists,⁵⁴ and the North American Menopause Society⁶ agree that persons with osteoporosis (bone mineral density T score of less than -2.5) or low bone mass and hip or vertebral fractures should receive treatment. These guidelines also suggest that persons with T scores higher than -1.5 should not receive therapy unless there is clinical evidence of osteoporosis. Thus, controversy remains regarding the indications for treatment among people with mild reductions in bone density. The guidelines include oral bisphosphonates among the first-line therapies for osteoporosis but do not name specific FDA-approved drugs.

RECOMMENDATIONS

The patient described in the vignette is at high risk for additional fractures on the basis of her history of vertebral compression fracture and a bone mineral density T score in the osteoporosis range. A drug with efficacy in preventing hip and spinal fractures is required, and I would treat the patient with either alendronate or risedronate for 5 years. After 5 years of treatment, I would decide whether a drug holiday might be appropriate for this patient, taking into consideration the fact that she is at high risk for recurrent fracture. I would suggest a calcium intake of 1200 mg per day from dietary sources, with calcium supplements as a second choice. I would also measure the serum 25-hydroxyvitamin D level and select an appropriate level of vitamin D intake, encourage regular weight-bearing exercise, and emphasize the importance of adherence to procedures for taking the medication. I would use measurements of bone mineral density to monitor her response to therapy 12 months after treatment is initiated and then at 24-month intervals as needed. A decline in bone mass or another low-trauma fracture would require careful review of the treatment plan and possible selection of another agent.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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