Adverse Effects of Bisphosphonates: Implications for Osteoporosis Management

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On completion of this article, you should be able to: (1) recognize and, when possible, identify patients at risk of adverse effects of bisphosphonate therapy, (2) counsel patients about the risk of bisphosphonates relative to the risk of osteoporotic fracture as estimated by the World Health Organization fracture risk assessment tool, and (3) critique the optimal dose and duration of bisphosphonate therapy for osteoporosis.

Bisphosphonates are widely prescribed and highly effective at limiting the bone loss that occurs in many disorders characterized by increased osteoclast-mediated bone resorption, including senile osteoporosis in both men and women, glucocorticoid-associated osteoporosis, and malignancies metastatic to bone. Although they are generally well tolerated, potential adverse effects may limit bisphosphonate use in some patients. Optimal use of bisphosphonates for osteoporosis requires adequate calcium and vitamin D intake before and during therapy. The World Health Organization fracture risk assessment algorithm is currently available to determine absolute fracture risk in patients with low bone mass and is a useful tool for clinicians in identifying patients most likely to benefit from pharmacological intervention to limit fracture risk. This fracture risk estimate may facilitate shared decision making, especially when patients are wary of the rare but serious adverse effects that have recently been described for this class of drugs.

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BMD = bone mineral density; CTX = carboxy-terminal collagen cross-links; FDA = Food and Drug Administration; FRAX = fracture risk assessment; GI = gastrointestinal; IV = intravenous; ONJ = osteonecrosis of the jaw

The widespread introduction of bisphosphonates into clinical practice, which occurred after Food and Drug Administration (FDA) approval of alendronate in 1995, was largely driven by the use of this class of skeletal antiresorptive agents to treat postmenopausal osteoporosis. A wealth of information from well-designed clinical trials clearly shows that, as a class, bisphosphonates are highly effective at limiting the loss of bone mass, deterioration of bone microarchitecture, and increased fracture risk that occur with aging. Additional approved indications for bisphosphonates currently include other forms of osteoporosis (such as that which occurs in men or is associated with glucocorticoid therapy), Paget disease of bone, hypercalcemia of malignancy, and metastatic bone disease.

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Some adverse effects that may occur with bisphosphonate therapy, such as gastroesophageal irritation, were recognized early on. Other more serious potential complications, including osteonecrosis of the jaw (ONJ) and severe suppression of bone turnover, have only more recently been appreciated and reflect the relative rarity of such adverse effects. This concise review addresses the short-term, long-term, common, and rare adverse effects associated with bisphosphonate therapy. Other important considerations associated with bisphosphonate therapy, including the importance of ensuring adequate calcium and vitamin D intake, the availability of the World Health Organization fracture risk assessment (FRAX) algorithm[1] for estimating absolute fracture risk, and uncertainty about the dose and duration, are also discussed.

BASIC BISPHOSPHONATE PHARMACOLOGY

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate. Because of their affinity for the major constituent of bone (hydroxyapatite), they are incorporated into sites of active osteoclast-mediated bone resorption on the bone surface, allowing them to achieve a high concentration at local sites, where they can affect osteoclast activity. Bisphosphonates not bound to the skeleton are rapidly cleared from the circulation via renal elimination. They are extremely hydrophilic and are only poorly absorbed from the gastrointestinal (GI) tract (<1% for an oral dose). Once absorbed, skeletal retention is thought to reflect host factors (including the prevalent rate of bone turnover that determines binding site availability and renal function that determines clearance of unbound bisphosphonate) and bisphosphonate potency for bone matrix.[2]

Early-generation bisphosphonates (etidronate, clodronate, and tiludronate) are distinguished from later-generation bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronate) by the lack of a nitrogen-containing side chain. This difference accounts for the ability of nitrogen-containing bisphosphonates to inhibit bone resorption by 100- to 10,000-fold more than the non–nitrogen-

containing etidronate. The remainder of this review focuses on bisphosphonates that contain nitrogen because they are currently the most widely used in clinical practice. Maximal reduction in biochemical markers of bone resorption typically occurs within 3 months of initiating oral bisphosphonate therapy and remains approximately constant thereafter with bisphosphonate continuance.[3] Suppression of resorption occurs even more rapidly after intravenous (IV) bisphosphonate therapy. The duration of suppression parallels bisphosphonate potency for osteoclast inhibition, such that administration of a single 5-mg dose of the potent IV bisphosphonate zoledronic acid to postmenopausal women leads to continued suppression of biochemical markers of bone resorption 2 years after drug administration.[4] Although the precise biological half-lives of nitrogen-containing bisphosphonates in bone remain poorly characterized, it is estimated to be at least 10 years.[5]

SHORT-TERM ADVERSE EFFECTS OF BISPHOSPHONATE THERAPY

Upper GI Adverse Effects

Upper GI adverse effects are the most commonly cited reason for patient intolerance to oral bisphosphonates. As originally described, this association was thought to be due to erosive esophagitis resulting from suboptimal administration in patients who failed to maintain an upright posture for 30 to 60 minutes after ingesting medication with a full glass of water. Currently, most health care professionals are aware of this concern and counsel patients accordingly. Nonspecific GI symptoms, however, are still a prevalent reason for oral bisphosphonate discontinuation. The relationship between oral bisphosphonates and GI symptoms has been examined in multiple studies, which have consistently shown that the incidence of nausea, dyspepsia, abdominal pain, and gastritis is not significantly different between alendronate,[6] risedronate,[7] or ibandronate[8] and placebo. Thus, although GI symptoms are common, it should be recognized that both clinicians and patients have been sensitized to the potential for oral bisphosphonates to cause GI symptoms and may be biased toward making this association.

Key point: Except in situations in which clinical judgment suggests otherwise (eg, Barrett esophagus, altered gastroesophageal anatomy or dysmotility, expected nonadherence to safe pill ingestion), oral bisphosphonate therapy should be attempted without anticipating GI adverse effects. If a questionable association is made, a rechallenge with either the same or another agent may be attempted. Patients with well-controlled GI symptoms, such as gastroesophageal reflux treated with a proton pump inhibitor, may tolerate oral bisphosphonates better than patients with uncontrolled or long-term GI symptoms.

Acute Phase Reaction

In patients who receive IV bisphosphonate therapy, a transient acute phase reaction may occur; it usually lasts 24 to 72 hours and is characterized by fever, myalgias, and arthralgias. Clinical trials of IV zoledronic acid suggest that approximately 1 in 3 patients experiences such a reaction with the first infusion, but that the incidence declines progressively with subsequent infusions (1 in 15 patients with a second infusion and 1 in 35 patients with a third infusion).[9] This adverse effect was also observed in 1 in 10 patients receiving IV ibandronate.[10] Although much less common with oral bisphosphonates, this reaction may occur, especially after initiation of therapy. This reaction is idiosyncratic and thought to reflect the activation of γδ T cells. Treatment with acetaminophen may ameliorate these symptoms, which otherwise spontaneously resolve.

Key point: Patients should be aware of this potential adverse effect and notify their physician if symptoms are severe or persist longer than 72 hours. A mild reaction does not preclude future bisphosphonate therapy.

Severe Musculoskeletal Pain

Although all oral and IV bisphosphonate preparations list musculoskeletal pain as a potential adverse effect in their prescribing information, the FDA recently issued an alert highlighting the possibility of severe and sometimes incapacitating bone, joint, and/or musculoskeletal pain that may occur at any point after patients begin taking a bisphosphonate.[11] Although discontinuation of bisphosphonate therapy improves symptoms in some patients, others appear to have slow or incomplete resolution. Risk factors for and the incidence of this potential adverse effect of bisphosphonates are unknown.

Key point: Rarely, bisphosphonates can cause severe musculoskeletal pain. In patients who present with such symptoms, consideration of temporary or permanent drug discontinuation should be considered.

Hypocalcemia

Transient hypocalcemia with secondary hyperparathyroidism is a recognized but underappreciated consequence of bisphosphonate administration. Because of the limited absorptive potential of oral bisphosphonates, hypocalcemia occurs most frequently after IV infusion and appears to occur most often in patients with hypoparathyroidism, impaired renal function, hypovitaminosis D, limited calcium intake, or high rates of osteoclast-mediated bone resorption (such as Paget disease of bone or a large skeletal tumor burden). In a study that measured levels of serum calcium in patients with cancer complicated by bone metastases, total serum calcium levels declined an average of 2 mg/dL (to convert to mmol/L, multiply by 0.25) at 7 days and

nearly 3 mg/dL at 21 days after infusion of 4 mg of zoledronic acid.[12]

Key point: All patients who are to begin receiving either oral or IV bisphosphonate therapy should have adequate calcium and vitamin D intake. If any concerns about nutritional status or absorptive capacity arise, serum levels of 25-hydroxyvitamin D, calcium phosphorus, and parathyroid hormone as well as urinary calcium excretion should be assessed and abnormalities addressed before initiating bisphosphonate therapy.

Esophageal Cancer with Oral Bisphosphonates

As described in a recent letter from an epidemiologist at the FDA, the use of oral bisphosphonates also appears to be associated with an increased risk of esophageal cancer.[13] From its approval of alendronate in 1995 through mid-2008, the FDA received reports of 23 patients taking alendronate who were diagnosed as having esophageal cancer, with a median time from use to diagnosis of 2.1 years. Reports of 31 patients from Europe and Japan showed that, in addition to alendronate, esophageal cancer occurred in patients prescribed risedronate, ibandronate, and etidronate, with a median time to diagnosis of 1.3 years.

Key point: It remains unknown whether esophageal cancer results from nonadherence to prescribing directions, leading to esophageal irritation or erosion, and whether this association will persist after further study. Because several of the affected patients had preexisting Barrett esophagus, physicians should avoid prescribing oral bisphosphonates to patients with known esophageal pathology pending further data.

Ocular Inflammation

Although rare, ocular inflammation (eg, uveitis, conjunctivitis, episcleritis, and scleritis), ocular pain, and photophobia have been shown to occur with both oral and IV bisphosphonate therapy. Onset is again idiosyncratic and can occur weeks, months, or even years after bisphosphonate initiation.

Key point: Given the complexity of diagnosis and treatment, ophthalmologic referral is recommended for patients with eye symptoms potentially related to bisphosphonate therapy.

LONG-TERM ADVERSE EFFECTS OF BISPHOSPHONATE THERAPY

Osteonecrosis of the Jaw

No potential adverse effect of bisphosphonate therapy has been more widely reported in the popular and clinical literature than ONJ. Current estimates of ONJ related to oral bisphosphonate therapy for osteoporosis are approximately 1 in 10,000 to 1 in 100,000 patient-years, although notably this estimate is based on incomplete data.[14] The incidence of ONJ in patients with cancer, who typically receive high doses of IV bisphosphonates with a dosing schedule that is much more frequent than that used for other conditions, has been estimated to be 1 to 10 per 100 patients. Poor oral hygiene, invasive dental procedures or denture use, and prolonged exposure to high doses of IV bisphosphonates appear to increase the risk of ONJ development.[15] Care for ONJ is largely supportive, with antiseptic oral rinses, antibiotics, and limited surgical debridement as necessary. Performance of a careful oral examination for active or anticipated dental issues and discussion of the importance of maintaining good oral hygiene after starting treatment may be helpful in limiting the risk of ONJ development. A recent retrospective study suggested that antibiotic prophylaxis before invasive dental procedures may reduce the incidence of ONJ in patients with multiple myeloma treated with high-dose IV bisphosphonate therapy,[16] but additional studies are required both to verify this finding and potentially to extend it to other patient populations treated with bisphosphonates.

Recently, measurement of the bone resorption marker carboxy-terminal collagen crosslinks (CTX) has been recommended in the oral surgery literature as a method for estimating the risk of developing ONJ. In their report of 30 cases of ONJ associated with oral bisphosphonate use, Marx et al[17] suggested that serum CTX levels be used to stratify patients receiving bisphosphonate therapy as having low, moderate, or high risk of developing ONJ. Unfortunately, the described report did not include any control patients who were receiving bisphosphonates but did not have ONJ, nor were any indices of bone remodeling on any patient before bisphosphonate initiation available. Thus, although it is possible that serum CTX measurement may be a useful adjunct in considering how to manage a patient who presents with ONJ, available data do not support serum CTX testing for identification of patients who may be at increased risk of ONJ.[18] Further, discontinuation of bisphosphonate therapy in patients at increased risk of fracture until a serum CTX value reaches a predefined threshold value may lead to an increased risk of fracture.

Key point: Data do not support using serum CTX for ONJ risk assessment. In patients with substantially increased risk of fracture (due to previous fractures or on the basis of FRAX determination before beginning bisphosphonate therapy), physicians should ensure that alternative strategies for dental care have been discussed with the patient's dentist and that the patient understands the best estimate of risk of ONJ development. In patients at low risk of fracture (such as in primary prevention), stopping therapy for 3 months periprocedurally is unlikely to substantially

alter fracture risk or lead to bone loss but may help patients' peace of mind. Patients should be aware that no evidence shows that such stoppage will limit ONJ risk, which is already low in nearly all patients except those receiving frequent IV dosing in oncologic treatment regimens.

Atrial Fibrillation

Atrial fibrillation has recently been a concern with bisphosphonate use, as was first reported in the HORIZON Pivotal Fracture Trial.[9] In this study, a statistically significant increase (relative risk, 1.3% vs 0.5%) in the incidence of serious atrial fibrillation (defined as events leading to hospitalization or disability or judged to be life-threatening) was noted in patients receiving yearly IV zoledronic acid vs placebo. Rates of serious and nonserious atrial fibrillation were similar. Subsequent analyses of data from the Fracture Intervention Trial[19] suggested alendronate use may be associated with a slightly increased risk of atrial fibrillation, but this finding was not confirmed in other large studies of alendronate[20] or risedronate.[21] To date, no convincing mechanism has been proposed to account for this potential risk, nor has an effect of dose or duration on the proposed association been shown. This lack of association was noted in the final FDA statement released in November 2008, which recommended that health care professionals "should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their bisphosphonate medication."[11]

Key point: No clear association between atrial fibrillation and bisphosphonate use has been established. Patients receiving bisphosphonate therapy are primarily older and represent the population most likely to have atrial fibrillation independent of bisphosphonate use. Patients who are currently receiving bisphosphonate therapy are advised to continue their medication as prescribed.

Severe Suppression of Bone Turnover

In 2005, Odvina et al[22] reported on 9 patients who sustained atypical fractures, including some with delayed healing, while receiving alendronate therapy. These authors raised the concern that long-term bisphosphonate therapy might lead to oversuppression of bone remodeling, an impaired ability to repair skeletal microfractures, and increased skeletal fragility. However, case reports such as these are hard to generalize to patient care because these patients were exposed to varying doses of bisphosphonates, could have been taking other medications that affect bone (eg, glucocorticoids), or may have had another undiagnosed abnormality of bone before beginning bisphosphonate therapy. Two studies of long-term alendronate use failed to show an increased risk of fracture or abnormalities of bone remodeling after 10 years of therapy.[23,24] With fewer than 1000 total patients (including less than 5% who underwent bone biopsy that would detect excessive suppression with a high degree of sensitivity), however, it remains plausible that in rare cases some patients may experience an unexpected response to long-term bisphosphonate therapy.

Key point: If an adverse effect of bisphosphonate therapy in bone (eg, difficult-to-explain fractures, especially if multiple; unexpected radiographic findings; impaired bone healing) is suspected, clinicians should consider the limitations of short-term clinical trials and subsequent extensions to capture rare adverse events. Such patients may benefit from referral to a metabolic bone specialist for further evaluation. Such an evaluation may include a labeled bone biopsy for histomorphometric analysis.

Subtrochanteric Femoral Fractures

As with other possible adverse effects, the association of subtrochanteric femoral fractures with bisphosphonate therapy was not identified in clinical trials. Although these bisphosphonate-associated fractures are uncommon, several case reports have described some of their typical clinical features. In addition to occurring in the proximal or midfemoral diaphysis, the fractures typically occur either spontaneously or result from low-energy trauma, are transverse or oblique (≤30°), have delayed healing, occur in patients who have received prolonged bisphosphonate therapy, and are often preceded by a prodrome of thigh pain, vague discomfort, or subjective weakness.[25,26] Imaging of the contralateral femur may show thickened cortices and the presence of a cortical stress reaction. Recently, the association between such fractures and bisphosphonates has been questioned, and these fractures were suggested to be merely an uncommon subtype of osteoporotic femur fracture[27] or a manifestation of a rare metabolic bone disease (adult hypophosphatasia) with coincident bisphosphonate exposure.[28]

Key point: Patients who are receiving bisphosphonate therapy and who have a subtrochanteric femoral fracture should be referred to a metabolic bone disease specialist. Radiographic examination of the femur should be considered in patients who are receiving bisphosphonate therapy and who report symptoms of pain that may be originating from the femur.

ADDITIONAL IMPORTANT ISSUES FOR OPTIMAL BISPHOSPHONATE USE

Role of Calcium and Vitamin D

Ensuring adequate calcium and vitamin D intake both before and after initiation of bisphosphonate therapy is an extremely important but frequently overlooked aspect of

providing optimal care of skeletal health. Vitamin D insufficiency is widely acknowledged to be prevalent in nearly all patient populations prescribed bisphosphonate therapy, particularly in the elderly, who are more likely to have limited sun exposure, reduced dietary intake, and renal impairment. Vitamin D levels below the optimal range limit dietary absorption of calcium, lead to secondary hyperparathyroidism with loss of skeletal calcium to maintain normocalcemia, contribute to falling risk in the elderly,[29] and blunt the bone mineral density (BMD) response and antifracture efficacy of bisphosphonates.[30] Although currently available data offer no consensus on optimal serum levels of 25-hydroxyvitamin D (the storage form of vitamin D that best reflects vitamin D status), a level of 30 ng/mL (to convert to nmol/L, multiply by 2.496) is generally considered adequate; vitamin D intoxication occurs only when levels are higher than 150 ng/mL.[31] The National Osteoporosis Foundation recommends an optimal calcium intake for both men and women younger than 50 years of 1000 mg/d, with an increase to 1200 mg/d for those 50 years and older.[32] It recommends 800 to 1000 IU/d of vitamin D for men and women 50 years or older. This recommendation likely applies to all adults as a minimum intake required for optimal bone health.

Key point: Bisphosphonates are most effective at limiting fracture risk when taken in conjunction with adequate calcium and vitamin D. All patients for whom bisphosphonates are considered should be counseled on this important requirement before and during bisphosphonate therapy.

Estimating Absolute Fracture Risk With the FRAX Algorithm

There is general agreement that, in patients with osteoporosis as defined by the World Health Organization criterion of a BMD T-score of –2.5 or less at the total hip, femoral neck, or lumbar spine, or in those who sustain a fragility fracture of the hip or spine, pharmacological therapy should be considered to limit the risk of future fracture. Less clear, however, is the optimal management of patients with low bone mass or *osteopenia*, defined by a T-score between –1 and –2.5. Because BMD is only 1 risk factor for fracture, it cannot adequately capture the heterogeneity in fracture risk that exists across patient populations.

To address this discrepancy, the World Health Organization developed an algorithm (FRAX) that allows calculation of absolute 10-year probabilities of sustaining any major osteoporotic fracture (defined as clinical vertebral, hip, forearm, or humeral).[1] The algorithm uses both femoral neck BMD and clinical risk factors (all of which can be readily determined in an office visit) that have been shown to affect the risk of fracture independently of BMD. Importantly, the FRAX algorithm is intended only for postmenopausal women and men 50 years and older. In addition, it applies only to patients who have not previously received pharmacological treatment. When combined with an estimate of the relative risk reduction that therapeutic intervention can provide, the degree to which an individual's risk of fracture would be altered with pharmacological intervention can be assessed. The algorithm is freely available and allows physicians and patients to make more informed decisions on the basis of potential risk of fracture without treatment vs the benefits and potential adverse effects of different therapeutic agents, including bisphosphonates.

Key point: The FRAX algorithm[1] is appropriately used to assess the absolute 10-year risk of fracture in treatment-naïve postmenopausal women with osteopenia and men 50 years and older. It is easy to use and can facilitate dialogue between physicians and patients and help inform shared treatment decisions.

OPTIMAL DURATION OF BISPHOSPHONATE USE

The Fracture Intervention Trial Long-term Extension (FLEX), in which postmenopausal women who had received alendronate therapy for 5 years were randomized to continue receiving alendronate for 5 additional years or switched to placebo, provided clinical evidence that the effect of bisphosphonate therapy was maintained after discontinuation of therapy.[23,24] This is consistent with the prolonged skeletal half-life of bisphosphonates in general. Although the length of skeletal retention differs depending on the agent, such differences are of uncertain clinical importance for guiding duration of therapy. Drug holidays are becoming common practice for some patients, particularly those at relatively low risk of fracture. Although limited data are available to guide practice, monitoring for offset of effect and consideration for reinitiation of treatment are generally recommended. Patients in whom bisphosphonate therapy is discontinued are typically followed up with BMD measurements at 1- to 2-year intervals, with some experts advocating periodic measurement of biochemical markers of bone turnover (eg, serum CTX) to detect loss of the antiresorptive effect. These unanswered questions may also be relevant to IV bisphosphonate use; a recent study noted that the antiresorptive effects of zoledronic acid last more than 12 months, raising the question that zoledronate could be administered less frequently than annually.[33]

Key point: The optimal dose and duration of bisphosphonate administration for osteoporosis are unclear once treatment extends beyond the duration of placebo-controlled trials. The clinical scenarios in which bisphos-

phonates are used are heterogeneous. Furthermore, patient factors, including revised goals for care, may well change over an extended period of follow-up. Once treatment has extended beyond the duration of placebo-controlled trials, patients will be suboptimally treated by a strictly uniform approach.

CONCLUSION

Bisphosphonates have transformed the clinical care of an array of skeletal disorders characterized by excessive osteoclast-mediated bone resorption. Their widest clinical effect is shown in our current approach to the management of osteoporosis, in which bisphosphonates are considered first-line pharmacological therapy for most patients. Bisphosphonate therapy can be associated with mild adverse effects in some patients and, more rarely, with serious adverse effects. A discussion of these potential adverse effects with patients and other health and dental care professionals should begin with discussion of fracture risk that is the primary basis for their use. Because of their rarity and/or long latency, some adverse effects that have been associated with the use of bisphosphonates (including severe musculoskeletal pain, esophageal cancer, ocular inflammation, ONJ, oversuppression of bone turnover, and subtrochanteric femoral fractures) require health and dental care professionals to pursue a patient's symptom that might be a clue to the existence of an adverse effect. The informed and judicious use of bisphosphonates confers a clear clinical benefit in most carefully selected patients that outweighs potential risks associated with bisphosphonate use.

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CME Questions About Bisphosphonates and Osteoporosis

1. Which *one* of the following symptoms or physical signs is *least likely* to be related to the recent administration of an oral or intravenous (IV) bisphosphonate for the treatment of osteoporosis in an otherwise healthy patient?

   a. Conjunctivitis
   b. Perioral and digital paresthesias
   c. Bone pain
   d. Irregularly irregular pulse
   e. Fever and myalgias

2. A 55-year-old recently menopausal and otherwise healthy woman is found to have osteopenia on the basis of bone mineral density (BMD) screening by dual energy x-ray absorptiometry. On follow-up testing 2 years later, her BMD has substantially decreased despite optimization of lifestyle, including adequate calcium and vitamin D intake. She chooses to begin taking alendronate therapy for the prevention of osteoporosis and continues to receive this therapy with stable BMD and no fractures during the next 5 years.
   Which *one* of the following considerations regarding long-term bisphosphonate therapy is *true* in this patient?

   a. A drug holiday is required
   b. Imaging should include femur radiography to assess for femoral cortex changes that may precede a subtrochanteric hip fracture
   c. She is at low risk of developing osteonecrosis of the jaw (ONJ)
   d. A fracture while receiving bisphosphonate therapy should raise suspicion for excessive suppression of bone remodeling
   e. Duration of bisphosphonate therapy is dictated by clinical guidelines on the basis of clinical trials

3. Which *one* of the following statements regarding the World Health Organization fracture risk assessment (FRAX) tool for estimating absolute fracture risk is *true* when considering the risks and benefits of bisphosphonate therapy?

   a. The calculator estimates the risk reduction afforded by specific bisphosphonate treatment regimens
   b. An estimate of absolute fracture risk by the FRAX tool can inform a discussion of risks and benefits of bisphosphonate therapy
   c. The FRAX tool is required to identify patients at high risk of fracture who are most likely to benefit from bisphosphonate therapy
   d. The lumbar spine is the preferred BMD measurement site to enter in the FRAX risk calculator tool, given these fractures are consistently prevented by bisphosphonate therapy
   e. The FRAX tool allows for fracture risk estimates in patients of both sexes and all ages

4. Which *one* of the following statements regarding the role of calcium and vitamin D intake in the bisphosphonate-treated patient is *true*?

   a. Bisphosphonates reduce the requirement for nutritional calcium by decreasing bone remodeling
   b. Adequate vitamin D nutrition is needed only to reduce risk of fractures associated with falling
   c. Acute suppression of bone remodeling with bisphosphonates may result in hypocalcemia in patients with suboptimal calcium and vitamin D intake
   d. Increasing doses and potency of bisphosphonates has minimized the role of calcium and vitamin D intake in achieving optimal response to bisphosphonate therapy
   e. The current US recommended daily allowance for vitamin D (400 IU/d) is sufficient to achieve optimal 25-hydroxyvitamin D levels for bone health in US adults

5. Which *one* of the following statements regarding clinically important features of bisphosphonate action is *true*?

   a. Bisphosphonates have limited bioavailability when given intravenously because of rapid clearance by the kidney
   b. After incorporation into bone, bisphosphonates remain biologically active in vivo for years after discontinuation
   c. The degree and persistence of bisphosphonate-related suppression of bone remodeling are consistent within a population of osteoporotic patients over time
   d. Biochemical markers of bone remodeling, such as serum carboxy-terminal collagen crosslinks (CTX), specifically reflect bisphosphonate effects on remodeling in the jaw bones
   e. Adverse effects of bisphosphonates on bone can be readily detected by conventional radiography

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

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