CME CREDIT ***EDUCATIONAL OBJECTIVE:*** To clarify what is known about a possible association between the use of bisphosphonate drugs and the development of osteonecrosis of the jaw

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Bisphosphonates and osteonecrosis of the jaw: Innocent association or significant risk?

ABSTRACT

Published case series and systematic reviews have documented an association between bisphosphonates and osteonecrosis of the jaw. However, a cause-and-effect relationship has not been established, and most of the reported cases have been in patients with cancer who were receiving much higher doses than those used to treat osteoporosis or Paget disease of bone. The risk, if any, to patients with these latter conditions receiving these drugs appears to be very small.

KEY POINTS

Recently published data do not support the hypothesis that these drugs cause osteonecrosis of the jaw.

There is no evidence to support routine dental examinations for all patients before starting bisphosphonate therapy for osteoporosis or Paget disease, but heightened concern seems warranted for cancer patients.

Clinical experience suggests that dental work by experienced dentists and surgeons can be carried out safely with very little risk to patients taking bisphosphonates.

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Recent case reports have linked bisphosphonate drugs to osteonecrosis of the jaw, and these reports have been widely publicized. Many patients receiving these drugs are asking their dentists and doctors whether the drugs do more harm than good, and some have even stopped taking them against medical advice. Health care professionals may be unsure what to tell patients and may be fearful of litigation.

However, most of the cases reported were in cancer patients, who are at significantly higher risk of osteonecrosis of the jaw for several reasons, and who receive much higher doses of bisphosphonates than do patients with osteoporosis or Paget disease of bone.

Moreover, although case reports have clearly documented an association between these drugs and osteonecrosis of the jaw, there is a lack of robust scientific evidence to support a cause-and-effect relationship. In fact, well-controlled clinical studies have not shown an increased risk of this complication in patients with osteoporosis or Paget disease of bone who were exposed to these agents, nor have they elucidated definite pathogenic mechanisms by which it might occur.

For these reasons, we believe that patients with osteoporosis should be advised of:

- Their risk of fracture
- The significant risk of morbidity and death following such a fracture
- The effectiveness and excellent safety of bisphosphonate therapy in preventing fractures
- The evidence that such therapy for osteoporosis and Paget disease poses little or no risk of osteonecrosis of the jaw

- The need for further research.

WHAT IS OSTEONECROSIS OF THE JAW?

Osteonecrosis—a general loss of bone tissue as a result of cell death[1]—can occur at any skeletal site, but it typically involves the long bones, ie, the femur, tibia, and humerus.

Osteonecrosis of the jaw is a rare disorder characterized by exposure and loss of bone in the maxillofacial complex. It can result in significant morbidity and can be resistant or refractory to conventional therapy.

This condition is not new, having been described in 19th century factory workers exposed to white phosphorus used in matchstick manufacturing. Known then as "phossy jaw," it was associated with poor dentition and often resulted in severe disfigurement, disease, and death. Use of white phosphorus, and matches containing it, were subsequently banned in many countries.[2]

In the early 20th century, radiation therapy for cancers of the head and neck area came into vogue, but its side effects included damage to the skeleton, or osteoradionecrosis.[3] In 1950, LaDow[4] described a case of osteoradionecrosis of the jaw and reviewed the literature available at that time. He concluded that there were three main causes of osteonecrosis of the jaw, namely, radiation therapy, trauma, and infection.

Many patients are asking whether the drugs do more harm than good

Although many such cases have since been reported in association with radiation therapy, chemotherapy, or both, and involvement of other skeletal sites is well described,[5–8] the actual incidence of osteoradionecrosis in the general population remains unclear because no large epidemiologic studies to elucidate accurate numbers have been published.

BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW

Bisphosphonate-associated osteonecrosis of the jaw is a relatively new condition, having been first reported in three case series[9–11] published in 2003 and 2004. The patients had exposure of areas of alveolar bone, mostly after oral surgery, eg, mucogingival flap elevation procedures (such as tooth extraction), that did not respond or were refractory to conventional treatment. All had received a bisphosphonate drug.

After these articles were published, the number of reported cases rose dramatically, including a case presented by one of us.[12] By the end of January 2008, more than 500 papers on this condition were listed in PubMed. More than 60% had been printed since 2003, and approximately 85% concerned the association between osteonecrosis of the jaw and bisphosphonate use (search terms: "osteonecrosis of the jaw" and "bisphosphonate").[13]

Although some dentists and oral surgeons claim to have seen many patients with this disorder, physicians who specialize in osteoporosis and metabolic bone disease do not. The medical literature and popular press have suggested that bisphosphonates are the cause of this malady. However, such articles are more perspective than evidence, as they are not scientific studies but rather reports of cases or series, or reviews of these. High-impact journals have given such articles prominent positions, highlighting the issue further, rather than balancing what is known and what is not known.

Thus, medicine safety boards, physicians, dentists, and oral surgeons have become increasingly concerned about the possible risk of this disorder in their patients on long-term bisphosphonate therapy, prompting organizations to issue management guidelines for this disorder and regulatory bodies to mandate warning labels on all drugs in this class about the possible risk.[14–18] Funding agencies have highlighted this as an area in need of further investigation.[17]

However, robust evidence of a causal relationship is lacking. Contributing to the problem, other disorders can have similar presentations.

As a result, the diagnosis requires a dental examination and dental imaging, which are often impossible or impractical in a medical setting. Well-designed studies have relied on blinded panels of dental specialists using clinical and imaging data to adjudicate cases as osteonecrosis of the jaw before including them in published reports; case reports, however, often do not.

TABLE1

Differential diagnosis of osteonecrosis of the jaw

CONDITION	ETIOLOGY	SIGNS AND SYMPTOMS
Alveolar osteitis (dry socket)	Partial or total loss of blood clot in extraction site	Area of exposed bone around extraction socket Pain, often radiating through side of head and ear Foul odor
Gingivitis	Soft-tissue inflammation in response to plaque bacteria, biofilm	Gingival inflammation (red, swollen, rounded margins; bleeding upon manipulation)
Periodontitis	Loss of attachment (periodontal ligament, alveolar bone, cementum) as a host-modulated immune response to plaque bacteria, biofilm	Gingival inflammation Radiographic evidence of alveolar bone loss Foul odor
Periapical pathology	Pulpal-periapical response to infection of the dental pulp (eg, caused by caries)	Possible gingival inflammation, gingival sinus tract Radiographic evidence of periapical lesion
Osteonecrosis	Unclear	Variable signs and symptoms may include some or all of the following: pain, swelling, paresthesia, suppuration, soft-tissue ulceration, intraoral or extraoral sinus tracts, loosening of teeth, radiographic variability

HOW IS OSTEONECROSIS OF THE JAW DIAGNOSED AND MANAGED?

A working definition of osteonecrosis of the jaw has recently emerged, and it will likely continue to evolve as results of further investigation become available.

A confirmed case is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after being identified by a health care provider, in a patient who is currently receiving or has been exposed to a bisphosphonate and who has not had radiation therapy to the craniofacial region.[14,17] This 8-week duration is consistent with the time frame in which soft tissue would be expected to close and exposed bone would be expected to heal under normal conditions after oral surgery such as dental extraction or a flap elevation procedure.

The working definition is one of inclusion and exclusion because the clinical presentation of osteonecrosis of the jaw is very similar to that of other diseases (TABLE 1).[14,17] It is important for health professionals to understand this, since patients who have established osteonecrosis of the jaw or who are deemed to be at risk of it can also present with these other common clinical conditions that should not be confused with it.

Patients may have no symptoms at the time of presentation. However, symptoms can include oral or jaw pain, difficulty chewing, evidence of infection, and dental loss. Bone loss is often apparent radiographically, and it may be focal or generalized. Other imaging studies such as cone beam computed tomography provide greater detail on the extent and nature of the lesions, and thus provide a better assessment.

Histologically, there is evidence of necrosis, cell death, and, usually, concomitant infection.[9–12,17]

Established osteonecrosis of the jaw can be difficult to treat and refractory to usual therapies

Management can be difficult

Osteonecrosis of the jaw can be difficult to manage, and extensive guidelines have been published.[14–17] Its treatment is complicated because resection of the necrotic area often only makes the necrotic area bigger. Unlike in osteoradionecrosis, surgical removal of the affected area often results in necrosis at the margins of resected

TABLE 2

Recommended treatments for osteonecrosis of the jaw, by stage

STAGE	DESCRIPTION	TREATMENTS
Stage 1	Exposed bone that is asymptomatic with no evidence of any significant adjacent or regional soft tissue inflammatory swelling or infection	Antibacterial rinse: chlorhexidine digluconate Clinical follow-up Patient education Symptomatic therapy
Stage 2	Exposed bone with associated pain, adjacent or regional soft-tissue swelling or secondary infection	Symptomatic treatment Pain control Superficial debridement Antibiotics (eg, penicillins, clindamycin), depending on laboratory culture results
Stage 3	Exposed bone associated with adjacent or regional soft-tissue inflammatory swelling or secondary infection and the presence of an extraoral cutaneous fistula or pathologic fracture	Antibacterial rinse Antibiotic therapy Pain control Surgical debridement Currently under investigation: Hyperbaric oxygen chamber dives Surgical bone-grafting, bone stimulation agents and growth factors, tissue-engineering Parathyroid hormone preparations

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bone. This creates a potential situation of "chasing" affected bone in procedure after procedure, which results in significant morbidity.

Staging guidelines provide a framework for treatment (TABLE 2).[14,16] Some case studies suggest that mucoperiosteal flap elevation procedures such as bone grafting, the use of bone morphogenic proteins, and alveolar bone decortication can succeed, but no randomized, placebo-controlled trials have been conducted.[19] Treatment with analgesics, antibiotics, surgery, and hyperbarbic oxygen may also be beneficial. Most authors have concluded that prevention is the ideal approach.[14–20]

A preventive protocol for cancer patients

Most of the cases reported so far have been in cancer patients receiving long-term treatment with potent bisphosphonates in high intravenous doses (12 times the usual dose for osteoporosis) after a mucoperiosteal flap elevation dental procedure (many of which were performed on an emergency basis).[9–12,14–20] Authors have thus concluded that a preventive protocol should be followed for all patients being considered for intensive bisphosphonate treatment, similar to that adopted for patients receiving head and neck radiation.

Specifically, all chronic dental and periodontal conditions should be identified and stabilized before starting intensive bisphosphonate therapy. Experts today believe that controlling all chronic dental problems before starting intensive intravenous bisphosphonate therapy may be the best method to avoid dental surgery after bisphosphonate therapy has begun, particularly since the washout period (time to elimination of the drug) for bisphosphonates in alveolar bone is unknown.[14–20]

Although authors seem to agree that such a preventive protocol is prudent for intensive intravenous therapy, it does not appear to be necessary for patients without cancer.[14,17] Indeed, such an approach is impractical, given the huge numbers involved and the lack of evidence to support it.

WHAT ARE BISPHOSPHONATES, AND WHY THE CONCERN?

Bisphosphonates are analogues of pyrophosphates, inorganic compounds developed to remove calcium carbonate from water in industrial pipes and laundry machines. Pyrophosphate use in humans arose from their affinity for calcium phosphate, which proved beneficial in scintigraphic imaging studies and in preventing tartar build-up, resulting in their incorporation into toothpastes. Modifications of the pyrophosphate molecule led to the development of diphosphonate compounds (later known as bisphosphonates), which have gained widespread use in treating a variety of disorders of the skeleton and of calcium metabolism.

These drugs prevent bone resorption by selectively inhibiting osteoclastic activity through several mechanisms (depending on the compound), thus helping prevent bone loss, bone pain, and hypercalcemia in diseases of the skeleton.

Bisphosphonates are widely used

Today, oral and intravenous bisphosphonates are widely prescribed for several skeletal disorders, including metastatic disease, malignant hypercalcemia, Paget disease of bone, and prevention and treatment of osteoporosis.[21–23]

More than 10 million Americans and more than 200 million people worldwide may have osteoporosis, which results in more than 1 million fractures each year. The lifetime risk of fracture for a postmenopausal white woman today is approximately 40% (approximately 15% for a 50-year-old man), and her annual risk of fracture is greater than her combined risk of stroke, heart attack, and breast cancer.[22] Several bisphosphonates have been shown to safely and significantly reduce the risk of fracture in patients with osteoporosis and to be effective therapies for Paget disease of bone.[24–31]

Bisphosphonates are the most widely prescribed drugs for osteoporosis,[22,23,29] with almost 200 million prescriptions for oral bisphosphonates worldwide. As of 2004, exposure to alendronate (Fosamax) was estimated to be about 20 million patient-years.[32] Noncompliance limits their effectiveness in practice, due in part to concerns about adverse effects.

Since bisphosphonates are so widely prescribed, concern has been raised that they may be causing a new epidemic of osteonecrosis of the jaw.[9] However, most reported cases have been in cancer patients, who are known to be at increased risk of this condition and who receive doses of bisphosphonates up to 12 times higher than in patients with osteoporosis or Paget disease of bone.[9–12,33–38]

The optimal duration of bisphosphonate therapy for these diseases to obtain the maximum benefit and minimize cost and harm remains unclear. Although a recent report suggests a bisphosphonate "drug holiday" may be an option when treating postmenopausal osteoporosis, larger, more robust studies of longer duration are needed.[39] Outcomes of osteonecrosis of the jaw related to drug holidays have not been investigated.

'IF I TAKE THIS TO STOP BONE LOSS, WILL IT HURT MY JAWS?'

The recently described association between bisphosphonates and osteonecrosis of the jaw has received considerable attention. Guidelines have been drawn up, some based on the assumption that bisphosphonates cause the osteonecrosis, but not based on scientific research.[14–18] More than 90% of reported cases have been in cancer patients, a group known to be at increased risk of osteonecrosis of the jaw and other skeletal sites, for reasons that include radiation therapy, chemotherapy, corticosteroid use, and increased risk of infections.[4,6,9–12,33–38] Nevertheless, it has been assumed that these patients are the same as osteoporosis patients, and sometimes that causation is beyond dispute. This is problematic for two main reasons:

Some guidelines are based more on assumptions than on science

- Since noncompliance and lack of adherence (due to lack of knowledge about the dangers posed by osteoporosis, cost of the drugs, difficulty with dosing regimens, and fear of adverse effects) limit the effectiveness of these therapies in clinical practice, such attention has already persuaded patients to discontinue or refuse therapy (J.J. Carey, personal experience and communications from colleagues); and
- Patients with osteoporosis and osteoporotic fractures have increased rates of morbidity and mortality and significantly higher

fracture risk, which can be prevented with these agents if they are willing to take them.

Association does not prove causation

However, association does not prove causation. A relationship between a drug and a disease may be due to chance alone or to confounding factors.[40] To judge the exact nature of this relationship, several issues need to be considered when reviewing the available evidence.

Substantiating that an agent causes a disease requires careful consideration of several aspects of their relationship: temporality, strength, dose-response, reversibility, consistency, biologic plausibility, and specificity.[41] Correct interpretation of the strength of the evidence should also incorporate an evaluation of the study design, size, and reporting mechanism. Accordingly, case reports and case series are considered to constitute the weakest evidence, while randomized controlled trials and meta-analyses are usually considered the strongest.

The washout period for bisphosphonates in alveolar bone is unknown

When a true cause-and-effect relationship does exist, the situation can be a simple one in which only a single agent is involved. However, the issue can be decidedly more complex when the cause is an effect-modifier, requiring the interaction of additional factors.

When a cause has been assumed, demonstration of the dose-response relationship is also important: whether the risk is related in a continuous fashion to dose and duration of therapy (all patients), is seen only with particular doses or regimens (such as frequent use of high doses of potent bisphosphonates), or exists only in people who have passed a certain threshold value (for example, it may only occur in those who have received 0.5 g of an intravenous or 10 g of an oral bisphosphonate). Bearing in mind these considerations, the nature of the relationship between an agent and a disease can be better understood.[40–43]

A cause-and-effect relationship has not been established

A cause-and-effect relationship between bisphosphonates and osteonecrosis of the jaw has not been clearly established.[14,17] Although case series highlight a relationship between the two, large controlled trials evaluating the occurrence of osteonecrosis of the jaw as the primary outcome have not been conducted. To date, most cases have been reported as uncontrolled case series, generally considered the weakest form of evidence.[43]

Most cases have been in cancer patients

Most cases of osteonecrosis of the jaw were in patients with cancer (particularly breast cancer and multiple myeloma) receiving potent intravenous bisphosphonates in high doses, most of whom had other documented risk factors, including recent dental procedures such as tooth extraction.[9–12,15–19,33–38]

One of the most compelling studies supporting causation examined the prevalence of osteonecrosis of the jaw in a cohort of 303 myeloma patients from 1991 to 2003. Osteonecrosis of the jaw developed only in those taking bisphosphonates (28 of 254), and the risk appeared greatest in those treated with both zoledronic acid (Zometa) and thalidomide (Thalomid). The importance of additional chemotherapies, concomitant diseases, and baseline dental pathology was not described.[35] Biases, including channeling bias (in which patients who appear at increased risk of this rare condition also appear to be most likely to receive this medication), referral bias, and survivor bias, were not addressed in this paper or in others claiming that the risk is related to the type of bisphosphonate used and the duration of its use.[15,33–38]

A review of all cases of osteonecrosis of the jaw over a 5-year period in one institution (N = 163) found that only 17 (10%) were associated with bisphosphonate use, and all 17 patients had other risk factors, such as concomitant therapy for malignancy and recent dental surgery.[34] The authors' concern that longer follow-up may have shown a higher incidence of this problem is supported by the temporal relationship seen in other reports in which cancer patients with osteonecrosis of the jaw appear to have had higher cumulative doses of intravenous bisphosphonates than those without.[9–12,15,34,35,37,38] Unfortunately, only one study had a control group to highlight the incidence of osteonecrosis of the jaw in similar patients not treated with bisphosphonates.[35]

The incidence in cancer patients treated with intravenous bisphosphonates has been reported as between 0% and 11%, and the incidence is higher following dental procedures and with a greater duration of drug exposure.[11,14,15,17,35,38,44]

Interestingly, in a recent survey of oncologists prescribing bisphosphonate medications for metastatic indications, two-thirds said they believe their patients probably have undiagnosed chronic oral conditions that could increase the risk of osteonecrosis of the jaw following bisphosphonate therapy and dental surgery procedures. A similar number reported that their patients receive routine dental care (access to and cost of dental care and the difficulty in physician prescreening are cited as obstacles), but only about one-third actually refer their patients to dentists before starting bisphosphonate therapy.[45]

What recent studies in osteoporosis and Paget disease showed

Controlled scientific studies in osteoporosis and Paget disease of bone have not shown osteonecrosis of the jaw to emerge, even after years of treatment with bisphosphonate drugs.[24–31,46–49] To date, more than 50,000 patients have been treated with oral bisphosphonates—more than 100,000 patient-years for each drug: alendronate, risedronate (Actonel), and ibandronate (Boniva)—in clinical trials, and there has not been a single case of bisphosphonate-associated osteonecrosis in any of these studies.[48]

Recent publications have addressed the results of clinical trials comparing zoledronic acid (the drug most often associated with this condition in published case series) and risedronate in more than 300 patients with Paget disease of bone,[31] and with placebo in postmenopausal women with osteoporosis and persons over 50 years of age suffering a hip fracture treated for up to 3 years following their fracture.[29,30]

In the largest trial, almost 4,000 osteoporotic women were treated with 5 mg of zoledronic acid annually for 3 years, and a similar number received placebo. Despite a rigorous search for any potential cases of bisphosphonate-associated osteonecrosis of the jaw—adjudicated by a blinded panel of experts on the basis of clinical and dental diagnostic imaging—only two possible cases were found: one in the placebo group and one in the treatment group (a case of osteomyelitis that preceded any treatment with zoledronic acid). Both patients recovered following a course of oral antibiotics and debridement. There was no increase in osteonecrosis at other skeletal sites.[29,49]

Observational studies have yielded conflicting results. An Australian postal survey of oral surgeons and dentists combined with drug adverse events data suggested the frequency of osteonecrosis of the jaw was 1:2,260 to 1:8,470 in patients on weekly alendronate treatment for osteoporosis, and 1:56 to 1:380 in patients with Paget disease. Following dental extractions, this rose to 1:296 to 1:1,130 and 1:7.4 to 1:48, respectively. Results in patients with malignancy were similar to those in other studies.[44] The study raises issues similar to those in other studies: lack of an appropriate control group, reporting bias, and the possibility of multiple reportings of the same patients.

Unpublished information from pharmaceutical companies has suggested the incidence of unconfirmed cases of osteonecrosis of the jaw in persons taking alendronate is 0.7/100,000 person-years.[14,17] One study using administrative claims data did not find evidence of increased bisphosphonate use in patients undergoing jaw surgery (used as a surrogate for osteonecrosis of the jaw),[50] while another actually found that oral bisphosphonates had a protective effect against osteonecrosis of the jaw, inflammatory conditions of the jaw, and need for major jaw surgery.[51]

More than 50,000 patients in clinical trials received these drugs for osteoporosis or Paget disease, and none got osteonecrosis

The risk, if any, is probably very small

This information suggests that if these drugs, used at the recommended dose, really do pose a risk, it is probably very small: less than 1 case in 100,000 patient-years if taking an oral bisphosphonate such as alendronate.[14,17] This is significantly less than the risk of fracture in these patients (which may be higher than 1 in 10), the risk of death following such a fracture,[22–30] or the risk of death from drowning, house fire, or motor vehicle accident.[52]

The cases of osteonecrosis of the jaw that we have personally seen—all in cancer pa-

tients treated with chemotherapy and high-dose bisphosphonates—all showed histologic evidence of necrosis and concomitant infections, suggesting the actual diagnosis was osteomyelitis. Bone biopsies from affected but macroscopically normal mandibles at the time of surgical debridement for osteonecrosis of the jaw showed normal or increased osteoclastic activity, in contrast to what one would expect if there were oversuppression of bone turnover (unpublished data, J. Christian, J. Carey, Cleveland Clinic).

Recently, this family of drugs has shown some promise in limiting the progression of alveolar bone loss in periodontal disease (though they are not approved for this indication).[53–55] Finally, published studies suggest bisphosphonate therapy may even be beneficial in animals and humans with osteonecrosis,[56–58] and in conditions that mimic osteonecrosis such as SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) of the mandible, in which the histologic appearance may resemble that of osteonecrosis.[59]

WHAT SHOULD WE TELL OUR PATIENTS?

The risk is significantly less than the risk of death following a hip or vertebral fracture

Several things are worth emphasizing from the published data and guidelines:

- Many things are unknown about osteonecrosis of the jaw and the risk in people taking bisphosphonates.
- The best evidence today does not support a cause-and-effect relationship between osteonecrosis of the jaw and bisphosphonate therapy.
- If bisphosphonates are causative, the risk appears very low in patients without cancer.
- It is important to distinguish between cancer and noncancer patients because of different risk factors, the markedly higher doses of bisphosphonates used in cancer patients, and the much greater incidence of osteonecrosis of the jaw seen in cancer patients irrespective of the cause.
- The higher risk in cancer patients is likely modified or confounded by additional risk factors, possibly including long-term use of high-dose intravenous bisphosphonates.
- About 90% of cases of bisphosphonate-associated osteonecrosis of the jaw have been in cancer patients, in whom a substantial temporal relationship to bisphosphonate therapy has been seen.[9–12,15–17,19,49,54–57]
- Prevention will likely be the most effective management strategy because of the significant morbidity associated with and the refractory nature of osteonecrosis of the jaw.
- Prophylactic dental examinations and any needed repair work are probably best done before starting bisphosphonate therapy in cancer patients; however, studies supporting such a strategy are needed.
- There is no evidence to support routine dental examinations before starting such therapy for disorders other than cancer, or for stopping such therapy before, during, or after dental surgery. Whether this is true for patients who have been taking these drugs for several years or more is unclear.
- Good communication between patients and their physicians, dentists, periodontists, and surgeons will help provide them with the best possible care.

Clearly, much further research is needed on the causes, risks, diagnosis, and management of this disorder to optimize patient outcomes. ■

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