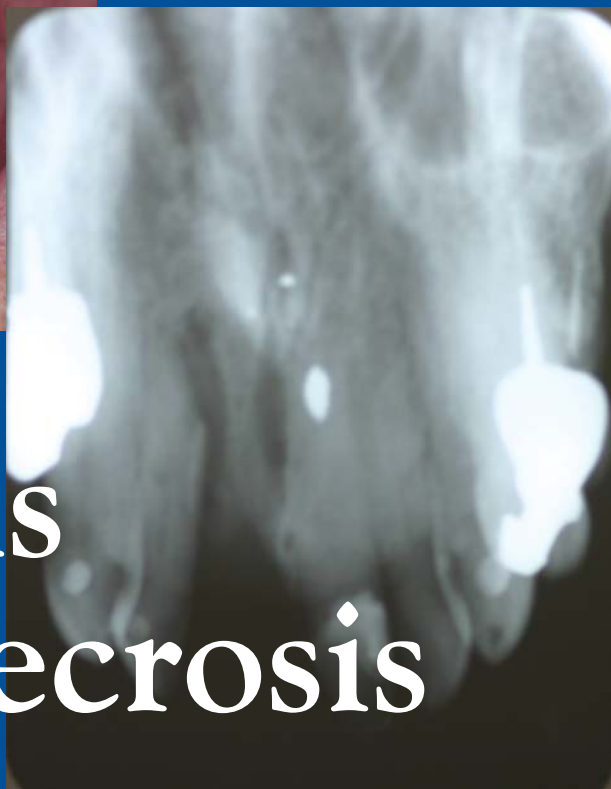


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Osteoporosis and Osteonecrosis of the Jaw

By Jon B. Suzuki, DDS, PhD, MBA, and
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Overview

Osteoporosis is a major public health concern that predisposes men and women to disabling and costly fractures. Over the next decade, as baby boomers age, this has the potential to become a problem of epidemic proportions. The U.S. census shows that the population is living longer. The National Osteoporosis Foundation (NOF) predicts that millions will be at risk for osteoporosis and low bone mass over the next 10 years.¹ Osteoporosis is underdiagnosed and undertreated at this time. There are several effective treatments that reduce the risk of osteoporotic fractures. Among these are the oral bisphosphonates.

In 2004, case reports of osteonecrosis of the jaw (ONJ), a rare complication, were reported in individuals receiving oral bisphosphonates for osteoporosis, although the majority of cases reported have been in patients with cancer receiving high doses of intravenous bisphosphonates.² Dental hygienists have an important role in discussing overall medical and dental health with patients. The incidence of ONJ is low with oral bisphosphonates, and this risk should be balanced against the benefits of osteoporosis therapy.

Learning Objectives

Upon completion of this course, the participant will be able to:

- Understand osteoporosis; the disease and its complications, incidence and economic impact.
- Identify agents used to treat osteoporosis.
- Better understand position papers published on the prevention and treatment of ONJ.
- Understand the importance of balancing the risk of ONJ with the need to prevent osteoporotic fractures.

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Osteoporosis and Osteonecrosis of the Jaw

By Jon B. Suzuki, DDS, PhD, MBA, and Andrea B. Klemes, DO, FACE

Introduction

OSTEOPOROSIS IS A MAJOR public health concern that predisposes men and women to disabling and costly fractures. It is estimated that 44 million women and men aged 50 and older in the United States are at risk for these fractures.¹ Osteoporotic fractures cause significant morbidity and mortality, and have a major impact on activities of daily life.

Bisphosphonates, as a class, reduce bone loss associated with diseases such as osteoporosis, Paget's disease, multiple myeloma and metastatic bone disease. By reducing bone loss, they can significantly reduce the risk of fractures.³ In the past few years, there have been case reports of osteonecrosis of the jaw (ONJ) in some patients using these agents, which has brought this issue to

the attention of dentists and dental hygienists. While it is important that oral care professionals be aware of ONJ, it is also important that they consider their patients' overall health status as well as their dental health.

Dentists and dental hygienists should be aware of their patients' risk of osteoporosis and fracture, so they can work with physicians and patients to weigh the risks and benefits of treatment. There are differences in ONJ incidence with low-dose oral bisphosphonate therapy compared with high-dose intravenous bisphosphonate therapy. The incidence of ONJ is very low with oral bisphosphonate use.⁴

Dentists and dental hygienists should be aware of their patients' risk of osteoporosis and fracture, so they can work with physicians and patients to weigh the risks and benefits of treatment.

Osteoporosis

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture.⁵

Bone tissue is constantly remodeled during a person's life by a coordinated process of resorption

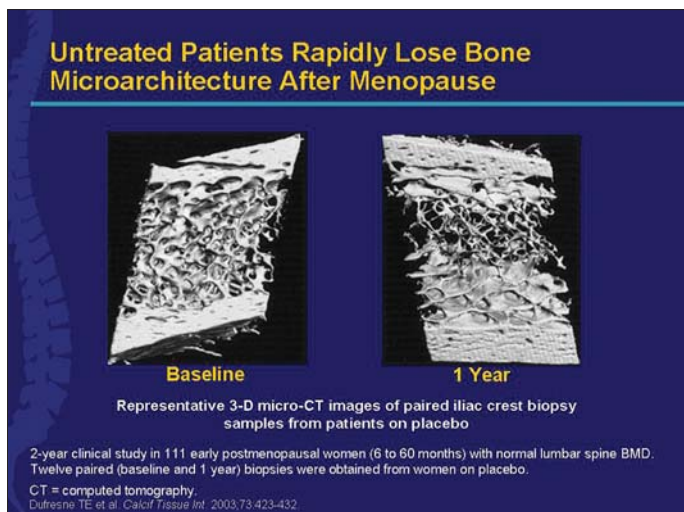


Figure 1.

by osteoclasts and formation by osteoblasts. In our younger years, there is a balance between these processes so that we either build bone mass or maintain it. This compromised bone strength is due to the fact that, as individuals age, the balance of bone remodeling changes in favor of resorption. In women, this process accelerates around menopause. This imbalance between resorption and formation leads to loss of bone mass (see Figure 1), predisposing individuals to an increased risk of fracture.⁶ It is commonly believed that osteoporosis is an inevitable part of aging, when, in fact, the disease can be prevented and treated.⁷

Osteoporosis has oral health implications. Loss of teeth and ridge resorption can occur in the mouth when a person has osteoporosis.⁸ It is important for dental hygienists to be aware of all systemic diseases and their effects on oral health.

Prevalence, Burden of Illness and Cost

Osteoporosis represents a significant public health problem that will increase as the world population ages.⁹ Osteoporosis and low bone mass affect 44 million women and men aged 50 and older in the United States. The 10 million people with osteoporosis and 34 million with low bone mass represent 55 percent of the people aged 50 and older. According to NOF, by the year 2010, it is estimated that over 52 million women and men in this same age category will either have osteoporosis or be at increased risk due to low bone mass. By the year 2020, NOF expects this number to increase to over 61 million. In the U.S. alone, osteoporosis causes 1.5 million fractures annually (Figure 2). These include 300,000 hip fractures, 250,000 wrist fractures, 700,000 vertebral fractures and 300,000 fractures at other sites (Figure 3). A woman's risk of hip fracture is equivalent to her combined risk of developing breast, uterine and ovarian cancer. Half of women and a quarter of men over the age of 50 will have an osteoporotic fracture before they die.⁹

Osteoporosis can have a serious impact on those affected individuals. The morbidity rate for one year in those who suffer an osteoporosis-related hip fracture is up to 22 percent (Figure 4).¹⁰ Some patients are unlikely to regain pre-fracture levels of mobility and independence. Approximately 50 per-

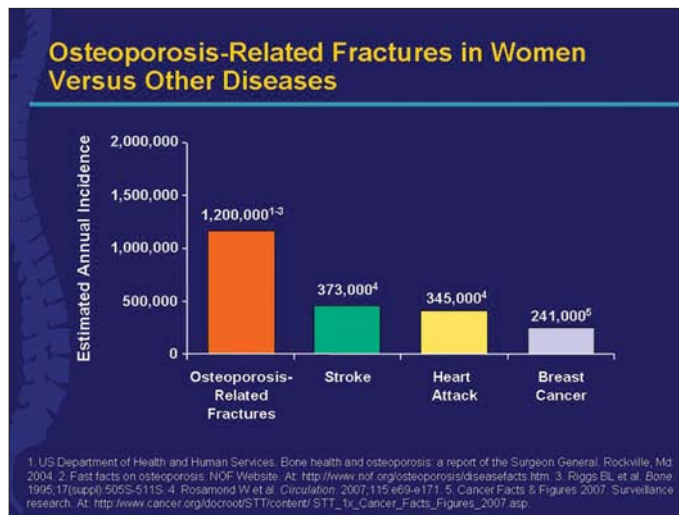


Figure 2.

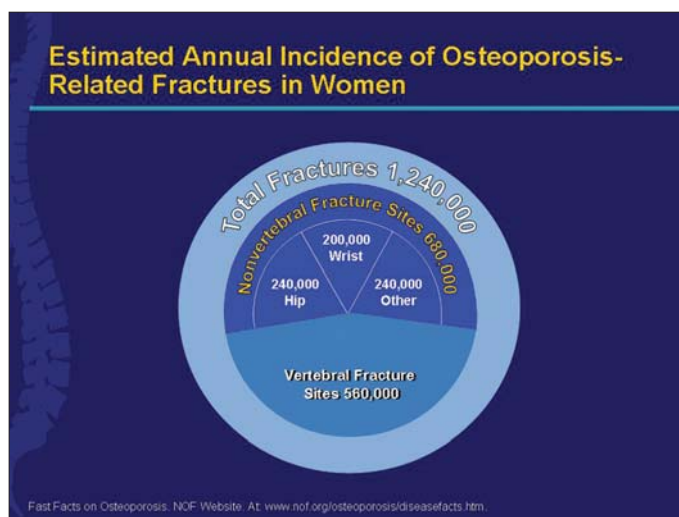


Figure 3.

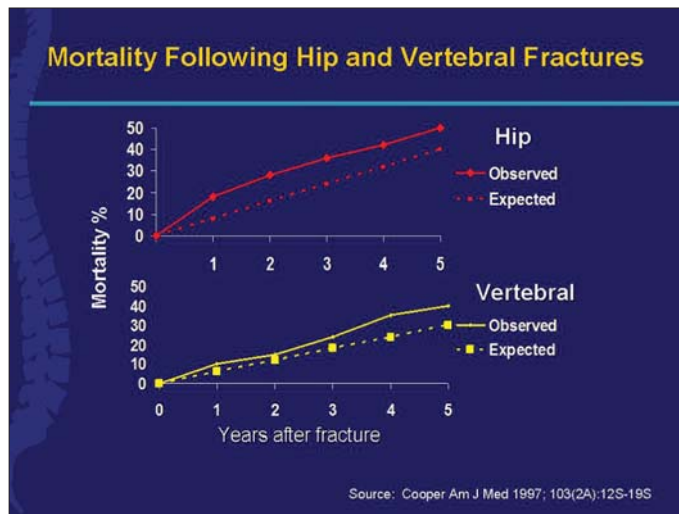


Figure 4.

cent of these are still unable to walk independently one year after their hip fracture, and 70 percent have difficulty with activities of daily living (e.g., dressing, personal hygiene, food preparation).¹¹⁻¹³

Vertebral fractures also have significant complications. Vertebral fractures can result in back pain, height loss and kyphosis,¹¹ and result in morbidity and mortality rates similar to hip fractures (Figure 4).¹³

Osteoporosis is a costly disease. It has been estimated that in the U.S. in 2005, there were more than 2 million osteoporotic fractures, resulting in direct costs (e.g., hospital and outpatient costs) of \$16.9 billion. Nonvertebral fractures, which occur at skeletal locations other than the spine, accounted for 73 percent of fractures and 94 percent of costs, with hip fractures in particular accounting for 14 percent of fractures and 72 percent of costs.¹⁴ Annual fractures and costs are projected to grow to more than 3 million fractures, costing \$25.3 billion in direct costs by 2025.¹⁴ In addition to direct costs, indirect costs are substantial and include lost productivity, which can impact patients and family caregivers.

Risk Factors

Factors that increase the likelihood of developing osteoporosis and fractures include a personal history of fracture after age 50, low body weight, current low bone mass, history of fracture in a first-degree relative (mother, sister etc.), female gender, being thin and/or having a small frame, advanced age, a family history of osteoporosis, menopause (especially early or surgically induced), Vitamin D deficiency, use of certain medications (corticosteroids, chemotherapy, anticonvulsants and others), low

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testosterone levels in men, cigarette smoking, excessive use of alcohol, or being Caucasian or Asian, although African Americans and Hispanic Americans are at significant risk as well.¹⁵

Women can lose up to 20 percent of their bone mass in the five to seven years following menopause, making them more susceptible to osteoporosis.¹⁵

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Treatments for Osteoporosis

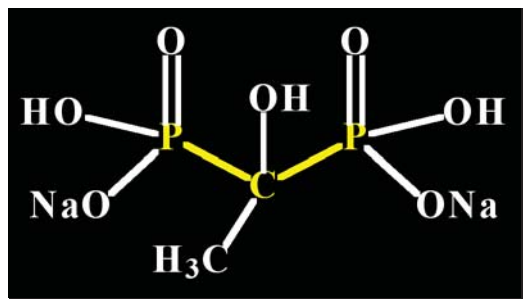
The goal in treating osteoporosis is preventing fractures. The drugs approved for treatment of osteoporosis have all been proven to reduce the risk of vertebral fractures. There is varying evidence on nonvertebral (usual sites include hip, wrist, clavicle, humerus, leg and pelvis) fracture protection as well as the speed at which these drugs reduce fracture risk.

There are four types of drugs presently approved for the treatment of osteoporosis: bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin and parathyroid hormone. The first three are anti-resorptive drugs; they affect the osteoclast function in resorbing the bone. Parathyroid hormone is an anabolic drug that builds bone.

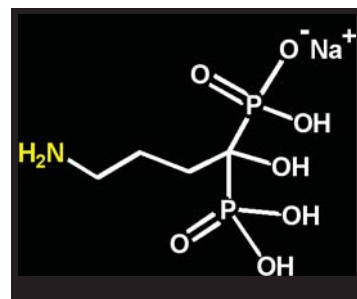
Oral Bisphosphonates

Bisphosphonates are stable analogs of pyrophosphates, which are naturally occurring modulators of bone metabolism.¹⁶ The chemical structure of bisphosphonates includes a P-C-P backbone that bestows a strong affinity for bone mineral and provides potent inhibition of bone turnover both in vivo and in vitro.¹⁷ Different bisphosphonates were developed by modifying the side chains, R1 and R2.

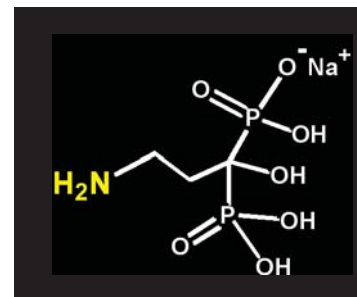
There are bisphosphonates that do not contain nitrogen in the R2 side chain (e.g., etidronate [Didronel®; Procter & Gamble Pharmaceuticals, Cincinnati, OH], tiludronate [Skelid®; sanofi-aventis, Paris, France], and clodronate [Bonefos®; Bayer Schering Pharma, Berlin, Germany]).



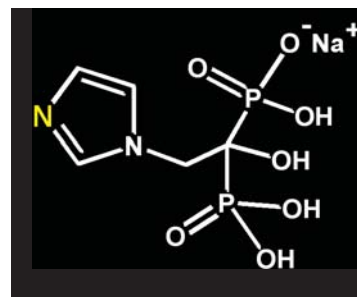
Etidronate



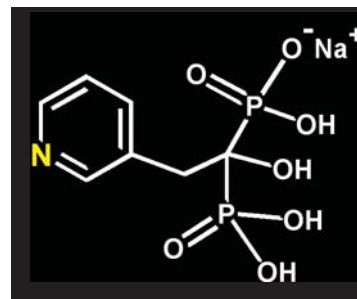
Alendronate



Pamidronate



Zolendronate



Risedronate

Those that contain nitrogen include alendronate [Fosamax®; Merck Pharmaceuticals, Whitehouse Station, NJ], pamidronate [Aredia®; Novartis Pharmaceuticals, East Hanover, NJ], zoledronic acid [Zometa®, Novartis Pharmaceuticals], ibandronate [Boniva®; Roche Pharmaceuticals, Nutley, NJ], and risedronate [Actonel®; Procter & Gamble Pharmaceuticals].

Bisphosphonates inhibit bone resorption by reducing osteoclastic bone resorption. Nitrogen-containing bisphosphonates are not systemically metabolized and are poorly absorbed with oral administration. Of the small amount that is absorbed (.06%), 50% is excreted unchanged in the urine, and the rest remains bound to bone, acting locally and then slowly released over time.

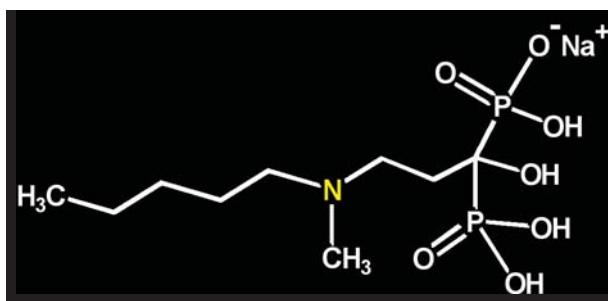
Differences between the bisphosphonates can be seen in the laboratory and in clinical practice. Each bisphosphonate has a unique profile of potency and binding to the bone.¹⁸

Benefits of Osteoporosis Treatment with Oral Bisphosphonates

The oral bisphosphonates currently approved by the U.S. Food and Drug Administration (FDA) for the prevention and treatment of osteoporosis are alendronate, ibandronate and risedronate. These three are the most widely prescribed therapies for osteoporosis. Data from randomized, placebo-controlled clinical trials indicate that all three of these agents reduce the risk of vertebral fractures, and that alendronate and risedronate reduce the risk of nonvertebral fractures.¹⁹⁻²⁵

Side Effects of Oral Bisphosphonates

The main short-term side effects associated with the use of nitrogen-containing oral bisphosphonates are gastrointestinal (GI). In prescribing information for all oral bisphosphonates, there are precautions for GI side effects, musculoskeletal pain and ONJ. Concerns have been expressed about the long-term safety of bisphosphonates due to their long half-life, prolonged reduction of



Ibandronate

bone turnover, and the potential for reduced bone quality and strength.²⁶ Long-term studies have followed patients treated with risedronate for up to 7 years and alendronate for up to 10 years.^{27,28} These studies suggest that prolonged treatment does not result in any loss of benefit or untoward side effects.

Osteonecrosis of the Jaw

History

Reports of ONJ first appeared in the literature in 2003 in letters to the editor and case reports related to the use of IV pamidronate and/or zoledronic acid for the management of oncological conditions: most commonly, multiple myeloma and metastatic breast cancer.²⁹⁻³¹ Further concerns about ONJ were raised in a retrospective chart review of 63 cases of ONJ among patients receiving intravenous bisphosphonates for the management of metastatic malignancies or oral bisphosphonates for osteoporosis.² Following these reports, FDA released a class precaution for all bisphosphonates, first IV formulations and then orals.³²

Reports of ONJ first appeared in the literature in 2003 in letters to the editor and case reports related to the use of IV pamidronate and/or zoledronic acid for the management of oncological conditions: most commonly, multiple myeloma and metastatic breast cancer.

A systematic review of the scientific literature in 2006 revealed that there were 368 reported cases of ONJ subsequent to the use of bisphosphonates.⁴ This review provided insight into the location of lesions, underlying diagnoses, type of bisphosphonate therapy and clinical observations associated with the phenomenon of ONJ. Most lesions affected the mandible and were mainly

located on the posterior lingual surface near the mylohyoid ridge. Nearly a third of cases were painless, and most were preceded by tooth extraction or another invasive dental procedure. Slightly more women than men were affected (with ratio of 3:2).⁴ These findings indicated that patients with multiple myeloma or breast cancer with bone metastases given intravenous pamidronate or zoledronic acid were at greatest risk for ONJ; these patients accounted for 94 percent of published cases. ONJ associated with the use of oral bisphosphonate use for osteoporosis was reported in 4 percent (15/368) of the cases.⁴

Since this time, there have been other literature reports, case reviews and position papers published.

Clinical Characteristics of ONJ

There is currently no universally accepted definition of ONJ. The manifestations are similar to those of osteoradionecrosis (ORN) – one key difference being that involvement of the mandible is extremely rare with ORN but occurs more commonly in ONJ.^{4,33} The clinical signs include failure of the bone and oral mucosa to heal over six to eight weeks, jaw pain or numbness, soft-tissue swelling and infection, loose teeth and exposed bone in the oral cavity. Development of a clear understanding of ONJ is further complicated by the fact that affected patients often have serious comorbidities (e.g., advanced malignancies, coagulopathies and diabetes mellitus) for which they may be receiving chemotherapy, corticosteroids or immunosuppressive agents.

Although there is a growing concern about ONJ among patients and health care professionals, the findings should be kept in perspective. The incidence of ONJ is different in patients receiving oral bisphosphonates for osteoporosis compared with patients receiving high doses of intravenous bisphosphonates for management of malignancy.³⁴

The risk with oral bisphosphonate therapy for osteoporosis is estimated between 1 in 10,000 and less than 1 in 100,000 patient-treatment years, whereas the estimated incidence of ONJ in patients receiving IV bisphosphonates with malignancy appears to range between 1 percent and 10 percent.³⁴

The incidence of ONJ is different in patients receiving oral bisphosphonates for osteoporosis compared with patients receiving high doses of intravenous bisphosphonates for management of malignancy

Prevention and Treatment of ONJ

The American Dental Association (ADA), the American Association of Oral and Maxillofacial Surgeons (AAOMS), the American Society for Bone and Mineral Research (ASBMR) and the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) have all developed positions on the prevention, recognition and management of ONJ.³⁵⁻³⁸ The lack of studies on the prevention and treatment of ONJ, however, means that current recommendations are based on clinical experience and the association's opinion rather than evidence from prospective trials.³⁹ These position papers are summarized in Table I on pages 10-11.

As the treatment for ONJ is limited, prevention remains important.^{35,36} In patients taking or considering bisphosphonate therapy, the approach to preventing ONJ is largely determined by the type of bisphosphonate therapy. Given the apparently low risk of ONJ among patients receiving oral bisphosphonates for osteoporosis, some initial guidelines have suggested that what is needed is maintenance of good oral hygiene and the same level of dental care recommended for the general population.³⁵⁻³⁸

Some health care professionals recommend dental evaluation before initiation of bisphosphonate therapy, including examination of dentures to ensure proper fit.^{35,36} There are no data available to suggest whether discontinuation of bisphosphonate treatment, prior to the procedure, reduces the risk of osteonecrosis of the jaw (see box).

The dentist, dental hygienist and physician should work together with the patient to discuss

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Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment, prior to the procedure, reduces the risk of osteonecrosis of the jaw. Clinical judgment should guide the management plan of each patient based on individual benefit/risk assessment.

the benefits and risks of bisphosphonate therapy for osteoporosis and develop a treatment plan.

Summary

Osteoporosis is a major health problem that causes significant morbidity and mortality. There are a great number of men and women at risk for this disease and its complications today, and it is estimated that there will be many more in the future. Dental hygienists should be aware of the risks and benefits of treating osteoporosis, and be prepared to explain for patients the skeletal effects—including the oral health effects—of the disease. They might also encourage patients to consult their physicians regarding the research supporting the effectiveness of bisphosphonate therapy, as well as the research linking it to ONJ under certain limited conditions. Dental hygienists are in the best position to advocate optimal preventive care both

Table I.
Summary of Position Papers on the Prevention, Recognition and Management of ONJ

	ADA	AAOMS
Case Definition	The typical clinical presentation of BON includes pain, soft tissue swelling and infection, loosening of teeth, drainage and exposed bone.	Current or previous treatment with a bisphosphonate; Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and No history of radiation therapy to the jaws.
Incidence	Oral incidence reported at 0.7 cases per 100,000 person-years	Oral bisphosphonates have been quoted at 0.7/100,000 person-years of exposure.
Recommendations prior to starting oral therapy		A comprehensive oral evaluation should be carried out of all patients about to begin therapy with oral bisphosphonates (or as soon as possible after beginning therapy).
Recommendations on oral therapy	For individuals who have taken an oral bisphosphonate for less than three years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary. For those patients who have taken an oral bisphosphonate for more than three years, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for three months prior to oral surgery, if systemic conditions permit. The bisphosphonate should not be restarted until osseous healing has occurred	Routine dental treatment generally should not be modified solely on the basis of oral bisphosphonate therapy
Do you stop oral bisphosphonates before surgery?	Discontinuation of oral bisphosphonates for a period of three months prior to and three months following elective invasive dental surgery may lower the risk.	
Do you perform surgery?	Elective dentoalveolar surgery does not appear to be contraindicated in this group.	Patients taking oral bisphosphonates who are undergoing invasive surgical procedures should be informed of the risk, albeit small, of developing BON. Alternative treatment plans consisting of endodontics instead of extraction and bridges and partial dentures versus implant reconstruction should be discussed with the patient. If extractions or bone surgery are necessary, conservative surgical technique with primary tissue closure should be considered.

ASBMR

A *confirmed* case of bisphosphonate-associated ONJ was defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region.

ESCEO

Exposed bone in the mandible, maxilla or both that persists for at least 8 weeks, in the absence of previous radiation and of metastases in the jaws.

The risk with oral bisphosphonate therapy is estimated between 1 in 10,000 and less than 1 in 100,000 patient-treatment years.

For oral bisphosphonates used to treat osteoporosis, the number of spontaneous reports of ONJ submitted to their manufacturers indicates a reporting rate of less than 1 per 100,000 patient-treatment years

Patients who are starting or continuing to take bisphosphonates need to practice good oral hygiene and have regular dental visits during which they can receive proper dental care. It is not necessary to recommend a dental examination before beginning oral bisphosphonate therapy or to otherwise alter routine dental management.

In osteoporosis patients, no specific interventions prior to starting bisphosphonate therapy are required except to encourage routine dental care

Patients taking oral bisphosphonates should have the same dental care (such as good dental hygiene and cleaning, routine fillings and root canal procedures) recommended for the general population.

There is no need to stop bisphosphonate therapy or to take special precautions.

Some physicians have suggested that a drug holiday from bisphosphonates may be beneficial but there is no evidence to support this.

Dental surgery should be limited to that required for good dental health, and undertaken only when more conservative non-surgical therapies are either not appropriate or ineffective.

If a patient receiving bisphosphonates requires surgery in the maxillofacial region, and risk factors such as diabetes or corticosteroid use are present, close follow-up is recommended, and the use of antibiotics and mouth rinses should be considered.

in the dental office and at home to preserve the oral health of all patients including those with and at risk for osteoporosis.

Treatment is essential to reduce the risk of osteoporotic fractures. Oral bisphosphonates are an important treatment option for patients with this condition. Post-marketing case reports of ONJ in individuals taking oral bisphosphonates are rare, and this risk should be balanced against the benefits of osteoporosis treatment. Patients should be encouraged to work with their dentist, dental hygienist and physician to identify the best treatment regimen for them.

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CE Questions

- Osteoporosis is responsible for more than ___ fractures in the U.S. annually
 - 1.5 million
 - 15 million
 - 34 million
 - 1.5 billion
- Nonvertebral fractures account for ___ % of fractures and ___ % of cost.
 - 14 and 72
 - 16 and 25
 - 73 and 94
 - 92 and 97
- Oral _____ are the most widely used therapies for the treatment of osteoporosis.
 - Estrogen
 - Bisphosphonates
 - Parathyroid hormone
 - Elemental Calcium
 - Vitamin D
- To date the most common site of ONJ lesions were observed in:
 - Posterior mandible
 - Anterior maxilla
 - Incisive canal
 - Alveolar portion
- Most cases of ONJ were seen after:
 - Bleaching
 - Filling
 - Invasive procedures (including tooth extractions)
 - Orthodontic braces
- 94% of documented cases of ONJ were in patients with what co-morbidity?
 - Diabetes
 - Hypertension
 - Cancer
 - Osteoporosis

7. What clinical signs are most commonly associated with ONJ?

- Failure of the bone and oral mucosa to heal over 6-8 weeks.
- Jaw pain or numbness
- Soft tissue swelling and infection
- Loose teeth
- Exposed bone in the oral cavity
- All of the above

8. The current reported rate of ONJ in IV bisphosphonate users is _____. The current reported rate of ONJ in oral bisphosphonate users is _____.

- 1% and 1%
- 1-10% and between 1 in 10,000 and less than 1 in 100,000 patient treatment years
- 94% and 1 in 100,000 patient treatment years
- 100% and 1 in 10 patient treatment years

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